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Grand Rounds

Prevention of Sudden Cardiac Death:

The Role of the Implantable Cardioverter-Defibrillator

Sunil K. Sinha, M.D.[1], Davendra Mehta, M.D., Ph.D.[2], and J. Anthony Gomes, M.D.[3]

Abstract

Sudden cardiac death, usually due to fatal ventricular tachyarrhythmias, results in the loss of 300,000 – 400,000 lives each year in the United States. Implantable cardioverter-defibrillator therapy has revolutionized both the secondary and, increasingly, the primary prevention of sudden cardiac death. In the last decade, subcutaneous pectoral implantation with transvenous lead placement has lessened perioperative risk considerably, raising the benefit/risk ratio for many candidates. As a consequence, the list of approved indications for implantable cardioverter-defibrillator therapy has expanded rapidly in recent years. Current devices offer tiered therapy utilizing bradycardia pacing, anti-tachycardia pacing, low-energy cardioversion, and high-energy defibrillation. Hybrid therapy, combining device, drugs and radiofrequency catheter ablation as required, has become the standard of care for reducing both appropriate and inappropriate shocks. As implantation rates continue to rise, so will the number of patients presenting with electrical storm. The dilemma of how our society will cope with the enormous projected costs of implantable cardioverter-defibrillator therapy has yet to be resolved.

Key Words: Sudden cardiac death, ventricular tachycardia, ventricular fibrillation, implantable cardioverter-defibrillator, tiered therapy, hybrid therapy, inappropriate shocks, electrical storm.

Introduction

Sudden cardiac death is defined as unexpected death from a cardiac cause occurring within one hour of the onset of symptoms (1). Nearly 50% of all deaths attributable to cardiovascular disease are sudden in nature, accounting for the loss of 300,000 – 400,000 lives annually in the United States (2). Sudden cardiac death is usually due to malignant arrhythmia; 80 – 90% of such deaths are due to ventricular tachyarrhythmias, while the remainder may result from bradyarrhythmias, asystole, or pulseless electrical activity (3). Evidence from community-based studies indicate that only 4 – 33% of people with out-of-hospital cardiac arrest survive to admission (4, 5). Consequently, implantable cardioverter-defibrillator (ICD) therapy has become an important option in both primary and secondary prevention of sudden cardiac death due to ventricular tachyarrhythmias.

Causes and Predictors of Sudden Cardiac Death

A number of diseases are associated with sudden cardiac death (Table 1). Epidemiologic data indicate that coronary artery disease (CAD) causes 80% of fatal arrhythmias (6), and the roles of myocardial ischemia or prior myocardial infarction (MI) in this regard are well established (7). Dilated cardiomyopathy and hypertrophic cardiomyopathy are responsible for an additional 10 – 15% of arrhythmic deaths (8). The other reversible and nonreversible diseases listed probably account for less than 5% of malignant arrhythmias (2).

Conventional, modifiable cardiovascular risk factors such as cigarette smoking, hypertension, diabetes mellitus, and dyslipidemia serve as easily identifiable markers of an increased risk of sudden cardiac death. However, their primary significance lies in their link to coronary artery disease, the predominant disease predisposing to sudden cardiac death, rather than as specific markers for immediate fatal

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[1] Clinical Cardiac Electrophysiology Fellow, [2] Director, Clinical Cardiac Electrophysiology Section and [3] Director, Consultative Services, The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to J. Anthony Gomes, M.D., Director, Consultative Services, The Zena and Michael A. Wiener Cardiovascular Institute, Box 1054, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

Adapted from a Cardiology Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY, on July 8, 2003, and updated as of June 2004.

TABLE 1
Diseases Associated with Sudden Death

Coronary artery disease (myocardial infarction/ischemia)
Nonischemic dilated cardiomyopathy
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Brugada syndrome
Long QT syndrome
Short QT syndrome
Complex congenital heart disease
Wolff-Parkinson-White syndrome
Valvular heart disease
Cardiac sarcoidosis
Myocarditis
Drug induced
Electrolyte/metabolic disturbances
Aortic dissection
Pulmonary embolism
Pulmonary hypertension

arrhythmia (2). Clinically, the degree of functional impairment, as categorized by the New York Heart Association classification, and the degree of left ventricular systolic dysfunction, as assessed by echocardiography, radionuclide scintigraphy, or radiocontrast ventriculography, are powerful predictors of the risk of death, whether it is arrhythmic or non-arrhythmic in nature (9–11). Invariably, an episode of aborted sudden cardiac death due to hemodynamically unstable sustained ventricular tachycardia or ventricular fibrillation unassociated with a reversible cause engenders the highest risk of sudden cardiac death (12, 13).

Standard 12-lead electrocardiography may reflect underlying structural heart disease or even help specify diseases of electrophysiological concern, including long QT syndrome (14), short QT syndrome (15), arrhythmogenic right ventricular cardiomyopathy (16), Brugada syndrome (17) and hypertrophic cardiomyopathy (18). Additional noninvasive testing, such as 24-hour Holter monitoring, can be useful in ascertaining the risk of sudden cardiac death, especially if nonsustained or sustained ventricular tachycardia (Fig. 1) is documented in certain high-risk subgroups, such as those with left ventricular systolic dysfunction and CAD (19).

Further methods of noninvasive testing have been evaluated. After MI, signal-averaged electrocardiography demonstrates high negative predictive value, but clinical utilization remains limited by its low positive predictive value (20–22). Studies of noninvasive tests focusing on the role of the autonomic nervous system, such as heart rate variability (23) and baroreflex sensitivity (24), have indicated relatively low accuracy as predictors of arrhythmic events. To date, other noninvasive tests evaluating electrocardiographic repolarization abnormalities, including QT-interval dispersion and T-wave alternans, have proven either inconsistent or lacking in applicability beyond specific high-risk groups (25).

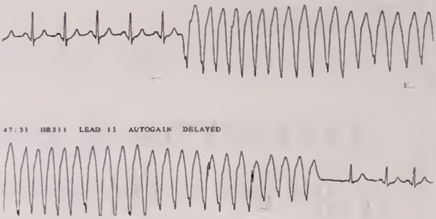

Fig. 1. Rhythm strip recording of sinus rhythm at 100 beats per minute with a 39 beat salvo of nonsustained ventricular tachycardia.

Electrophysiological testing continues to occupy a role in risk stratification for sudden cardiac death. Induced sustained ventricular tachyarrhythmia by programmed electrical stimulation is a well-established marker of increased risk of ventricular tachyarrhythmias (26, 27). However, electrophysiological testing remains limited by the significant proportion of false negative results that occur (19). Nevertheless, it remains a useful tool for evaluating patients with impaired left ventricular function and syncope (28) or nonsustained ventricular tachycardia (19, 29).

ICD Therapy: Rationale and Indications

In 1980, Dr. Michel Mirowski revolutionized the management of ventricular arrhythmias when he demonstrated the efficacy of the automatic implantable defibrillator (30). With the implantable cardioverter-defibrillator (ICD), once ventricular tachycardia or ventricular fibrillation is detected, an electrical current is directed across a large portion of the myocardium to depolarize most of the ventricular tissue, thereby allowing an organized rhythm to return. Despite initial criticism and considerable controversy (31), the ICD has gained widespread acceptance and implementation, with an estimated 55,000 such devices now implanted in the United States annually. This dramatic acceleration in implantation is a direct reflection of the rapidly expanding list of approved indications for ICD therapy in recent years (Table 2) (32).

Secondary Prevention

In 1997, the Antiarrhythmics Versus Implantable Defibrillators (AVID) study provided definitive proof of the superiority of ICD therapy over drug therapy for those patients at highest risk of sudden cardiac death—those who had already experienced an aborted cardiac arrest (33). This landmark multi-

TABLE 2

Indications for Implantable Cardioverter-Defibrillator Therapy

Class I (general agreement that it is beneficial, useful, and effective):

1. Cardiac arrest due to VF or VT not due to a transient or reversible cause.
2. Spontaneous sustained VT in association with structural heart disease.
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant, sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred.
4. Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a Class I antiarrhythmic drug.
5. Spontaneous sustained VT in patients without structural heart disease not amenable to other treatments.

Class IIa (weight of opinion is in favor of usefulness/efficacy):
Patients with left ventricular ejection fraction of ≤ 30% at least 1 month after MI and 3 months after coronary artery revascularization.

Class IIb (usefulness/efficacy is less well established by evidence/opinion):

6. Cardiac arrest presumed to be due to VF when electrophysiologic testing is precluded by other medical conditions.
7. Severe symptoms (e.g., syncope) attributable to ventricular tachyarrhythmias in patients awaiting cardiac transplantation.
8. Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome or hypertrophic cardiomyopathy.
9. Nonsustained VT with coronary artery disease, prior MI, and LV dysfunction, and inducible sustained VT or VF at electrophysiologic study.
10. Recurrent syncope of undetermined origin in the presence of ventricular dysfunction and inducible ventricular arrhythmias at electrophysiologic study when other causes of syncope have been excluded.
11. Syncope of unexplained origin or family history of unexplained sudden cardiac death in association with typical or atypical right bundle-branch block and ST-segment elevation (Brugada syndrome).

Adapted with permission from Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J A Coll Cardiol 2002; 40(9):1703–1719 (32).

LV = left ventricular
VF = ventricular fibrillation
MI = myocardial infarction
VT = ventricular tachycardia

center, unblinded, randomized controlled trial enrolled 1,016 patients resuscitated from near-fatal ventricular fibrillation or ventricular tachycardia (not due to reversible causes) with left ventricular ejection fraction (LVEF) < 40%, and assigned them to either ICD therapy or antiarrhythmic drug therapy (empirically administered amiodarone in 95.8% of cases). The trial was stopped prematurely when ICD therapy was shown to result in a significant survival advantage in comparison to antiarrhythmic drug therapy. The mortality rate in the ICD group was 24.6% vs. 35.9% in the antiarrhythmic group after 3 years of follow-up, yielding a relative risk reduction of 31%. The resulting average length of additional life associated with ICD therapy at 3 years was 2.7 months. However, one area of concern in the AVID study was the significant difference in beta-adrenergic blocker therapy between the ICD group (47.6%) and the antiarrhythmic group (18.9%), probably yielding some degree of survival advantage to the former. Similar results were reported in two smaller randomized trials, the Canadian Implantable Defibrillator Study (CIDS) (34) and the Cardiac Arrest Study Hamburg (CASH) (35). Details regarding the above-mentioned randomized control trials are provided in Table 3.

Primary Prevention

Unfortunately, only a small percentage of patients who suffer a cardiac arrest in the U.S. each year survive to benefit from an ICD for secondary prevention. Hence, ICD therapy for primary prevention of sudden cardiac death has become the focus of intense clinical investigation in recent years (Table 4). The first major study in this regard was the Multicenter Automatic Defibrillator Implantation Trial (MADIT), which included 196 patients with prior MI, LVEF ≤ 35%, nonsustained ventricular tachycardia (NSVT), and inducible sustained ventricular tachycardia upon electrophysiologic study not suppressible by intravenous procainamide (29). Follow-up over 5 years demonstrated a dramatic 41% relative risk reduction in mortality in the group randomized to ICD therapy as compared to the group given conventional therapy (including amiodarone). The Multicenter Unsustained Tachycardia Trial (MUSTT) included patients with CAD, LVEF ≤ 40%, NSVT, and inducible sustained ventricular tachycardia on electrophysiologic study (36). At five years, patients receiving ICD therapy experienced a mortality rate of 24% as compared to 55% for patients receiving antiarrhythmic therapy guided by electrophysiologic testing, and 48% for those patients treated with conventional therapy. More recently, the MADIT II study (37) compared 1232 patients with prior MI and LVEF ≤ 30%, without requiring documented NSVT or electrophysiologic testing, randomized either to ICD therapy or conventional medical therapy (including beta-adrenergic blockers and angiotensin-converting-enzyme inhibitors). After 20 months of follow-up, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group. In

TABLE 3

Trials of ICD Therapy and Secondary Prevention of Sudden Cardiac Death

Trial	Design	Participants	RRR
AVID (33)	Multicenter RCT comparing ICD to amiodarone in those with prior VT or VF and LVEF < 40%.	1016 enrolled	31%
CIDS (34)	Multicenter RCT comparing ICD to amiodarone in those with VF or hemodynamically significant VT or syncope and inducible VT on EP study, and LVEF < 35%.	659 enrolled	20%
CASH (35)	Multicenter RCT comparing ICD to amiodarone or metoprolol in those who had been resuscitated from VT/VF.	288 enrolled	23%

EP = electrophysiologic
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
RCT = randomized controlled trial
RRR = relative risk reduction (total mortality)
VF = ventricular fibrillation
VT = ventricular tachycardia

essence, one life was saved among every 11 implants. Accordingly, the United States Food and Drug Administration further expanded its list of approved indications for ICD therapy.

Not all studies have shown clinical benefit with ICD therapy (Table 4). The Coronary Artery Bypass Graft (CABG) Patch Trial randomized 1,055 patients with LVEF ≤ 35%, no prior ventricular tachycardia/ventricular fibrillation, and abnormal signal-averaged electrocardiogram scheduled for CABG surgery to either concomitant epicardial ICD implantation or only conventional medical management—excluding antiarrhythmic agents (38). ICD therapy did not improve survival, probably reflecting the important ben-

TABLE 4

Trials of ICD Therapy in Primary Prevention of Sudden Cardiac Death

Trial	Design	Participants	RRR
MADIT (29)	Multicenter RCT comparing ICD to antiarrhythmic therapy in those with prior MI, LVEF ≤ 35%, NSVT, and unsuppressible VT on EP study.	196 enrolled	41%
MUSTT (36)	Multicenter RCT comparing ICD to EP guided antiarrhythmic therapy or conventional therapy in those with CAD, LVEF ≤ 40%, NSVT, and inducible VT on EP study.	704 enrolled	50%
MADIT II (37)	Multicenter RCT comparing ICD to conventional therapy in those with prior MI and LVEF ≤ 30%.	1,232 enrolled	28%
CABG (38)	Multicenter RCT comparing ICD to conventional therapy in those undergoing surgical revascularization with LVEF ≤ 35%, and abnormal SAECG.	1,055 enrolled	None
DEFINITE (39)	Multicenter RCT comparing ICD to conventional therapy in those with non-ischemic dilated cardiomyopathy, LVEF < 36%, and PVCs/NSVT.	458 enrolled	30%
COMPANION (40)	Multicenter RCT comparing ICD/CRT to CRT to conventional therapy with either ischemic or non-ischemic dilated cardiomyopathy, LVEF ≤ 35%, and QRS ≥ 120 ms.	1,520 enrolled	36%

RRR = relative risk reduction (total mortality)
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
VT = ventricular tachycardia
CAD = coronary artery disease
PVCs = premature ventricular contractions
RCT = randomized controlled trial
MI = myocardial infarction
NSVT = non-sustained VT
EP = electrophysiologic
SAECG = signal-averaged ECG
CRT = cardiac resynchronization

efit provided by definitive surgical revascularization in reducing myocardial ischemia and improving left ventricular systolic function.

Primary prevention trials have also been undertaken to study patients with non-ischemic cardiomyopathy. Recently, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study was released (39). In it, 458 patients with non-ischemic cardiomyopathy, LVEF < 36%, NYHA I-III, and ventricular ectopy on Holter monitoring, were randomized to either conventional medical therapy or a single chamber ICD. After 29 months of follow-up, the DEFINITE study showed a significant 78.6% relative risk reduction in sudden cardiac death, but only a non-significant 30% relative risk reduction in overall mortality with ICD therapy (p=0.08). Previously, 2 smaller randomized trials, the Amiodarone versus Implantable Defibrillator in Patients with Non-ischemic Cardiomyopathy and Asymptomatic Non-sustained Ventricular Tachycardia (AMIOVIRT) study (40), and the Cardiomyopathy Trial (CAT) (41), had failed to show a mortality benefit with ICD therapy in the context of non-ischemic dilated cardiomyopathy. The relative lack of efficacy with ICD therapy in this group of patients may be due to the fact that the initiation of ventricular tachyarrhythmias in non-ischemic cardiomyopathy is often due to a focal autonomic mechanism rather than a reentrant mechanism (42). Hence, patients with non-ischemic cardiomyopathy may be more amenable to prophylaxis against sudden cardiac death with effective neurohormonal modulation alone (utilizing appropriate medical therapy). Data from the as-yet-unpublished Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) may help to further elucidate the role of prophylactic ICD therapy in patients with non-ischemic cardiomyopathy (43).

The results of the recently published Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial may provide the key to optimizing the efficacy of ICD therapy (44). In this trial, 1,520 patients with non-ischemic or ischemic (55%) cardiomyopathy, NYHA III-IV, LVEF ≤ 35%, and QRS ≥ 120 milliseconds, were randomized to optimal pharmacologic therapy alone or with cardiac resynchronization therapy (CRT—biventricular pacing) with either a pacemaker or ICD. After one year, CRT improved exercise tolerance and quality of life, and reduced mortality risk by 24%. More impressively, it reduced the relative risk of death by 36% (19.2% vs. 12.2%) when coupled with ICD therapy (Table 4). Therefore, it is likely that the benefits of CRT and ICD therapy are additive in patients with advanced heart failure and a prolonged QRS duration.

ICD Therapy: Implantation and Follow-up

ICD surgery in the 1980s and early 1990s required general anesthesia and prolonged hospital stays, and entailed a significant perioperative mortality rate (45). In that era, open thoracotomy was required for placement of epicardial patches tunneled to attach to the generator, the large size of which (> 200 cc) necessitated abdominal implantation.

In the 1990s, utilization of biphasic shock waveforms allowed for the development of active canisters (generators), which are smaller in size and do not require epicardial patches (46, 47). These smaller devices (~ 40 cc) can be implanted in the subcutaneous pectoral region, and the cephalic, axillary, or subclavian routes can be utilized (49) for transvenous right ventricular endocardial lead placement (Fig. 2). Accordingly, only local anesthesia and conscious sedation are required for device testing, hospital stays are short, and perioperative mortality rates are low (46–49).

The cardioverter-defibrillator lead is capable of bipolar sensing and pacing. It has at least one metal coil and is connected to the generator. A large charge of electricity, for shocking, can flow between this coil and the generator. The bulk of the generator consists of the battery (lithium silver vanadium oxide) that allows rapid discharge into a capacitor for shocks (50). Battery longevity ranges

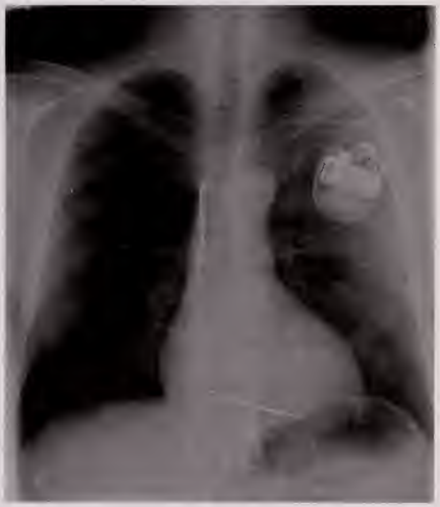

Fig. 2. Chest X-ray (posterior-anterior view) demonstrating a left pectoral implantable cardioverter-defibrillator with leads in the right atrium and at the right ventricular apex.

from 4–10 years, depending upon usage. Long-term elective follow-up usually consists of office visits approximately every 3 months. Routine visits include a focused history, measurement of vital signs, physical examination and recording of the patient's current medical regimen (50). In addition, a manufacturer-specific computer programmer is used to analyze the device, to check battery, capacitor and lead status, and retrieve data pertaining to tachycardia episodes and therapies (including intracardiac electrograms).

Tiered Therapy and Inappropriate Shocks

The present generation of programmable ICDs feature "tiered therapy," including anti-tachycardia pacing (ATP) for termination of monomorphic ventricular tachycardia, synchronized low-energy cardioversion, unsynchronized high-energy defibrillation and back-up bradycardia pacing. ATP therapies usually consist of "burst" or "ramp" pacing targeted to terminate ventricular tachycardia, usually due to a reentrant mechanism (Fig. 3). If the tachycardia is not successfully terminated after attempts at overdrive pacing, then a low-energy biphasic cardioversion (2–10 Joules) can be delivered. Ultimately, the ICD can deliver a high-energy biphasic shock (30–40 Joules) for the purpose of terminating ventricular tachycardia or ventricular fibrillation (Fig. 4). It is has become standard to forgo further ICD shocks following at least 5–6 sequential shocks for a refractory ventricular tachyarrhythmia (50).

One unique problem is that of preprogrammed ICD therapy delivery for benign or non-life-threatening tachyarrhythmias. Most commonly, sinus tachycardia or atrial tachyarrhythmia may result in a heart rate high enough to trigger detection and subsequent ICD therapy delivery resulting in a painful, inappropriate shock (Fig. 5). Strategies to combat such undesirable scenarios include concomitant drug therapy (such as beta-adrenergic blockers or sotalol), software reprogramming (enabling automatic mode switch for atrial fibrillation or atrial flutter), upgrading of the device's hardware (single to dual chamber sensing), and radiofrequency catheter ablation.

Hybrid Therapy

Since reducing the risk of sudden cardiac death is the ultimate goal, adjunctive antiarrhythmic therapy may be beneficial. In particular, sotalol has been shown to reduce mortality and both appropriate and inappropriate shocks following ICD implantation, as compared to placebo (51). It may be necessary to reevaluate ATP therapies or defibrillation thresholds following the introduction of new antiarrhythmic agents, especially amiodarone (52). Contemporary software allows for sophisticated, noninvasive electrophysiologic testing designed to induce, pace terminate, and cardiovert or defibrillate tachyarrhythmias. As well, scar-related (reentrant) ventricular tachycardia mapping and ablation is becoming increasingly practical and efficacious (53). Such interventional electrophysiologic techniques can be helpful to patients experiencing multiple ICD shocks due to recurrent monomorphic ventricular tachycardia or to those prone to a slow, incessant monomorphic ventricular tachycardia unamenable to device detection and therapy delivery.

Conclusions

The role of the ICD in the epidemiologic period of delayed degenerative diseases will inevitably continue

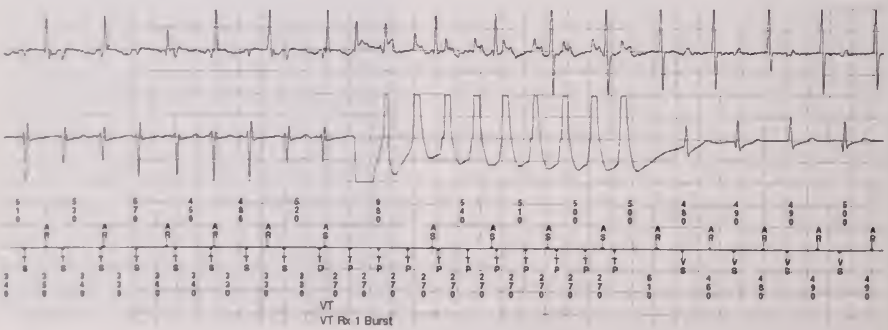

Fig. 3. Atrial (top) and ventricular (bottom) intra-cardiac electrograms indicating sinus tachycardia at approximately 115 beats per minute (top) and disassociated monomorphic ventricular tachycardia at 180 beats per minute (bottom). The ventricular tachycardia is successfully terminated by a 10 beat burst of rapid ventricular pacing.

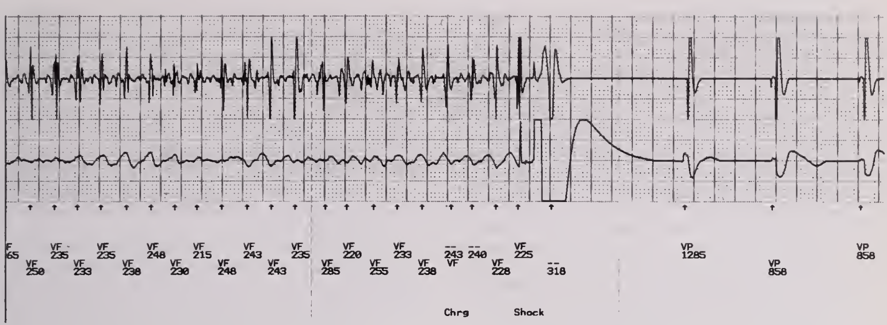

Fig. 4. Ventricular (top) and shock (bottom) intra-cardiac electrograms showing ventricular fibrillation successfully terminated by an internal biphasic shock (21 Joules) with resumption of ventricular pacing thereafter.

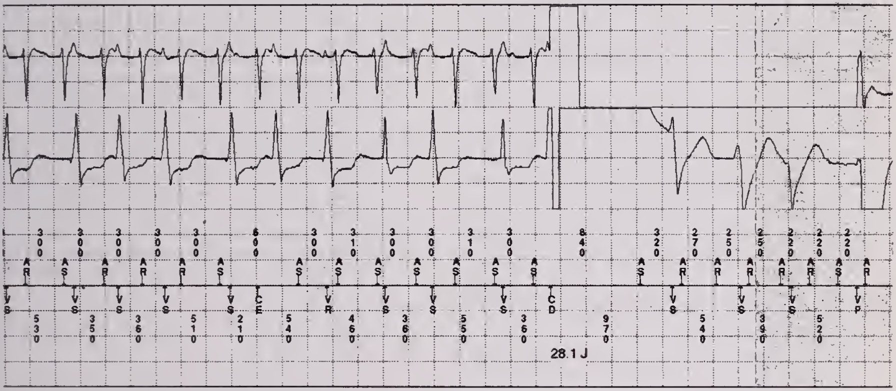

Fig. 5. Atrial (top) and ventricular (bottom) intra-cardiac electrograms indicating atrial tachycardia at 200 beats per minute (top) and variable 2nd degree atrio-ventricular block with an average ventricular response of 150 beats per minute (bottom) and the delivery of an "inappropriate" internal biphasic shock (28.1 Joules).

to grow and bring with it a number of medical, economic and social consequences. For appropriately selected patients, ICD therapy can prolong life for months or even years, but it does little to actually improve a patient's quality of life. The evolving role of concomitant biventricular pacing for patients with symptomatic left ventricular systolic dysfunction and intraventricular conduction delay has the potential to both improve functional status and lower mortality (54).

As the number of patients receiving ICD treatment continues to rise, so does the daunting prospect of more ICD patients presenting with "electrical storms." An electrical storm, defined as ≥ 3 shocks within a 24-hour period, can be difficult even for an experienced cardiac electrophysiologist to manage, and will pose an increasing challenge to our emergency rooms and coronary care units.

Finally, the cost of the ICD remains expensive (approximately $30,000 per device). In 2005, ICD therapy is projected to account for approximately $6.9 billion dollars, 0.4% of the U.S. national health care expenditure. This is a large sum for a nation already grappling with a sizable annual deficit and total debt. It has yet to be seen if our public institutions and private industry are capable of finding a solution that will be deemed affordable, practical, and fair to society as a whole.

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Grand Rounds

The Cardiac Consequences of the Obstructive Sleep Apnea-Hypopnea Syndrome

Stasia J. Wieber, M.D.

Abstract

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common disorder, estimated to occur in 4% of males and 2% of females in the workforce. This incidence increases with age. Obstructive sleep apnea-hypopnea is responsible for acute and chronic heart disease, but is a readily treatable disorder that is both underdiagnosed and underappreciated in health care. Because the cardiac consequences of untreated sleep apnea are so profound and the treatment relatively simple, the disorder needs to be recognized more frequently.

Key Words: Sleep apnea, obstructive sleep apnea, hypertension, heart, cardiac, arrhythmia, vascular.

What Is Obstructive Sleep Apnea-Hypopnea?

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by repetitive partial (hypopnea) or complete (apnea) closure of the upper airway during sleep. A common disorder, it is estimated to occur in 4% of males and 2% of females in the workforce (1). This incidence increases with age (2). Repetitive airway obstruction is associated with arterial oxygen desaturations, surges in sympathetic activity and/or short awakenings called "electrocortical arousals." But there is another feature of OSAHS that requires close attention by health professionals.

The association between OSAHS and cardiovascular disease was first observed in 1985 (3). Since then, studies have demonstrated a clear relationship between OSAHS and arterial hypertension (HTN), cardiac arrhythmias and pulmonary hypertension. Currently we are learning more about the immunological and vascular effects of OSAHS on the cardiovascular system.

Physicians should suspect OSAHS in patients with snoring and daytime somnolence and in those with unexplained hypertension or arrhythmias. Although OSAHS was first identified in obese men, one does not need to be obese or male to have the syndrome.

The diagnosis of OSAHS is made with a sleep study, formally called "nocturnal polysomnography" (NPSG). The patient is observed in a sleep laboratory overnight, where physiological parameters such as those recorded in an electroencephalogram (EEG), eye movements, respiration, heart rate, chest and abdominal movement, oxygen saturation and muscle activity are monitored. The most common and effective therapy is continuous positive airway pressure (CPAP), a form of noninvasive assisted ventilation that delivers air under pressure, which acts as a pneumatic "splint" to keep the airway open.

OSAHS and Hypertension

The prevalence of OSAHS in hypertension is 22–48%. The Sleep Heart Health Study indicated that the risk of HTN increases with escalating degrees of apnea or hypopnea (4). Nieto found that after adjusting for demographics and anthropometric variables, the odds ratio for hypertension for those with a high number of apneas ($\geq$ 30/hour) was 1.37 relative to those without apneas. This and other studies have confirmed that OSAHS is an independent risk factor for HTN.

OSAHS appears to cause both nocturnal and daytime hypertension. In 1993, Somers described surges in sympathetic discharge in the sural nerve

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Address all correspondence to Stasia J. Wieber, M.D., Assistant Professor of Medicine, Box 1232, Mount Sinai Medical Center, One East 100th Street, New York, NY 10029.

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after a Mueller maneuver, which is effectively an instance of apnea (5). In 1995, he described persistent sympathetic nerve activity increase during the day in patients with OSAHS, with further increases in blood pressure and sympathetic nerve activity during sleep (6). Hypertension in OSAHS is probably mediated by this enhanced sympathetic nerve activity. The mechanism is thought to involve stimulation of the peripheral chemoreceptors. These chemoreceptors, which are under neural control, are "reset" so that daytime hypertension persists.

Pepperell illustrated that treatment of OSAHS with CPAP produces an immediate or "first night" drop in blood pressure (7). He further demonstrated that blood pressure normalizes during the daytime after one month of therapy with CPAP. It is common to observe that patients with HTN and OSAHS who receive CPAP therapy often need less antihypertensive medication and are sometimes cured of their hypertension.

OSAHS and Arrhythmias

Even healthy humans are vulnerable to arrhythmias during sleep. Gulleminault noted 42 episodes of sinus arrest (lasting 2–9 seconds) in healthy adults during sleep (8). These cardiac events were not associated with OSAHS or significant oxygen desaturation. Individuals with ischemic heart disease are particularly vulnerable to arrhythmias, ST segment depression and T wave inversion.

Atrial arrhythmias and first- and second-degree atrioventricular block have been described in normal subjects during sleep (9). Brodsky monitored 24-hour continuous EKGs in 50 young, healthy males and observed pauses of up to 2.0 seconds in 30% of them (10). Tachyarrhythmias and bradyarrhythmias have been implicated as likely causes of cardiovascular morbidity in patients with OSAHS. The risk of arrhythmia with OSAHS appears to be related to sleep apnea severity. Analysis of electrocardiographic recordings of 458 patients with sleep apnea showed a 58% prevalence of arrhythmias in these patients (11).

CPAP as Therapy

CPAP reduces ventricular irritability in those with OSAHS and central sleep apnea (CSA). CSA is the condition in which absence of respiratory effort leads to cessation of breathing. Javaheri studied 29 patients with sleep apnea and left ventricular ejection fractions of less than 45% (12). Eight patients had OSAHS and 21 had CSA. All patients had stable compensated heart failure without changes in medical therapy for 4 weeks and at least 15 respiratory events per hour during sleep. In 55% of patients with heart failure and sleep apnea, the first night of CPAP eliminated sleep-disordered breathing and reduced ventricular irritability. Oxygen desaturations and the number of electrocortical arousals (short awakenings) were also reduced. It is known that both desaturations and arousals are associated with increased sympathetic nerve activity. Reduction of sympathetic nerve activity probably diminishes ventricular irritability. In addition, improved saturation may improve myocardial oxygen delivery.

Atrial Pacing as Therapy

Recently Garrigue reported 15 patients with heart failure and arrhythmia (9 patients with sinus node disease and 6 patients with brady-tachy syndrome), who had permanent atrial-synchronous ventricular pacemakers and underwent three consecutive sleep studies (13). The first night was a diagnostic night. Seven patients had OSAHS and eight patients had CSA. The patients were randomly assigned to undergo one of two sets of procedures on the second night and the other set on the third night. During one of the two nights, the basic ventricular rate of the pacemaker was programmed at 40 beats per minute, allowing the inherent atrial rhythm to be evident. During the other night, atrial overdrive stimulation was provided at the mean heart rate from the first night + 15 bpm. Interestingly, when patients had atrial overdrive pacing, there was a reduction of more than 50% in the number of apneas and hypopneas. Although this is a small study, it is intriguing to consider that atrial pacing may be beneficial for those with OSAHS.

Immunological and Vascular Effects of OSAHS

OSAHS affects platelet activation and augments adhesion molecules. These effects may have cardiovascular consequences. Spontaneous nocturnal platelet activation and platelet aggregation are both increased in patients with OSAHS (14). When CPAP therapy is initiated there is an immediate decrease in platelet activation and aggregation, suggesting that CPAP may diminish cardiac risk.

Circulating levels of adhesion molecules—intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin—are significantly increased in patients with moderate-to-severe OSAHS, compared with matched controls (15). These molecules mediate cellular interactions and transmigration of circulating leukocytes to the endothelial cells, one of the initial steps in the pathogenesis of atherosclerosis. It has not been determined if CPAP treatment diminishes the levels of these adhesion molecules.

Summary

OSAHS causes and exacerbates cardiovascular disease. This is probably because hypertension, arrhythmias and adverse vascular effects are increased in patients with untreated OSAHS. In patients with cardiovascular disease or essential hypertension, the diagnosis of OSAHS should be entertained. CPAP therapy is relatively noninvasive and reduces cardiovascular risk.

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White Coat Ceremony

"This above all . . ." Keynote Address

Barry Stimmel, M.D.

When I was first invited to speak, the instructions given to me by Dr. Smith were (a) be inspirational and (b) be brief. I therefore had to resist the temptation, in the current political climate, of advising you upon starting your first year of medical school to "bring it on" and sit down.

I realize that at this exciting time you are inundated with many facts, and it will not be easy to remember what is said in a setting such as this. Nonetheless, in the hope of promoting retention, I decided to relate a personal experience that describes two aspects of our behavior which, I truly believe, are essential to being a physician—yet are often forgotten, or worse, unconsciously manipulated to make us appear as less than we really are. These aspects are pride and respect.

First, I should state unequivocally that you have several reasons to be proud. It is not easy to be accepted into a medical school—especially a good one—and you are at one of the best. Second, you will be mastering a body of knowledge that will allow you to prevent diseases from occurring and to alleviate pain and suffering. However, it is all too easy for pride to turn into arrogance, manifested as a loss of respect. First a loss of respect for certain diseases, then perhaps a loss of respect for certain patients—and this can literally be deadly. This is not a hypothetical or theoretical danger, but is often recounted when patients describe their contact with some physicians. Most often, it can be seen by simply walking through an emergency room or clinic and observing the way some physicians relate to patients.

A number of years ago a study looked at students' attitudes in their first and senior years towards patients with AIDS and those with substance abuse problems (1). The study found that the feelings of first-year students with respect to treating AIDS patients were positive, and that these feelings did not diminish, but even improved slightly in the subsequent four years. But their feelings concerning treating persons with substance abuse problems actually deteriorated, with 78% stating they strongly disliked these patients and would avoid them.

This is not an isolated finding. People in pain often suffer needlessly because of physicians who are not uncaring—but are certain they know better as to when the patient is really in pain. Equally important, we tend to feel that people who do not meet our image of "solid citizens" do not tell us the truth. Numerous studies have documented that patients in underprivileged communities who suffer intense pain receive less medicine and less attention in emergency rooms and clinics than those who are more affluent. In addition to causing unconscionable suffering and distress, the adversarial relationships that often develop between physicians and patients are rationalized by physicians as being related to some inherent lack of worth of the patient rather than to their own behavior. To put it bluntly, these findings have suggested to many that some of these disparities in health care are due to conscious or unconscious racial bias or stereotyping on the part of the physicians (2–4).

Now, let me tell you a story that I hope will stay with you. It covers good and bad aspects of medical care encountered by a patient of mine.

The patient, a woman in my care for a number of years, was in her 40s and suffered from severe hypertension and diabetes. However, she had two other characteristics that put her at risk for not receiving the best of all possible care. First, she was markedly obese, and second, she was African American. One

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The following remarks were originally delivered to the Class of 2008, the Mount Sinai School of Medicine, New York, NY, on the occasion of the White Coat Ceremony, September 20, 2004.

Address all correspondence to Barry Stimmel, M.D., Dean for Graduate Medical Education, Professor of Cardiology, Box 1076, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: barry.stimmel@mssm.edu

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morning at approximately 3 AM, I received a call from her husband, who had been sitting in the emergency room with his wife for quite a long time. Well aware of the system at teaching hospitals, he had brought his wife into the emergency room following a party, as she had become distressed over developing some slurring of her speech. He had finally called me because, although the emergency room was not particularly busy, after being seen by the triage nurse, his wife had been seen by no one over the ensuing several hours. I asked to speak to the resident on call, who informed me that the triage nurse had screened the woman and felt that, since she had been out drinking and had perhaps had a little too much, they would wait for her to "settle down," so that a complete medical history and physical examination could be undertaken. I rapidly informed the resident that the woman did not consume alcohol on a regular basis and had brittle hypertension and diabetes. I insisted that they take her blood pressure and determine her blood glucose immediately, and call me back with the results. Unfortunately, I fell asleep and awakened within the hour realizing I had never received a phone call. I immediately went to the emergency room, just in time to see the resident running towards me, looking ashen and apologizing for what had happened. Despite knowing her history, since her arm was too large for the routine blood pressure cuff, both the nurse and the resident—certain of the validity of their initial impressions—became distracted and never bothered to obtain a larger cuff, until my patient seized and was then found to have a blood pressure of 220/170.

Unfortunately, she suffered a stroke. Upon seeing her and her husband that morning, I told her that the care she had received was far from adequate and that she certainly had the opportunity, if she wished, to seek legal redress. She replied that I had been caring for her for the past six years and that she had no desire to cause me or the hospital any problems. She just wanted to get better and to continue to have me provide her care. I reassured her that this would not be a problem. She recovered—almost fully—after spending a month in a rehabilitation facility prior to seeing me again in the office.

Now for part two: When she came to my office, she was furious. I asked her what was wrong, and she told me she had just received a letter from an attorney who had reviewed her entire chart and told her she could receive several million dollars without ever going to trial, due to the care that had been rendered. I reminded her that, in fact, I had told her the care was far from adequate. She replied, "That's not the point, Dr. Stimmel. I want to know how this person got hold of my record. Doesn't confidentiality apply to patients anymore?"

This, of course, was a very good question. I subsequently contacted the hospital legal staff, which in turn contacted the District Attorney's Office, which had a police detective impersonate my patient and meet with the attorney in question.

Let me pause for a moment to explain to you what happens when an adverse event occurs in any hospital. The records are always pulled and reviewed by an in-hospital committee to make certain that systems are put in place so that such an event does not recur. Then the chart is forwarded to the main insurance agency.

As it turns, out an individual at the insurance agency was taking "gold standard" cases of less-than-adequate care and farming them out to various attorneys in the city, including those at several prestigious law firms. Discover of this situation immediately initiated a criminal inquiry and, subsequently, a civil suit that forced a large number of law firms to return millions of dollars. The attorney responsible for releasing the records ultimately committed suicide.

Now, to the point of the story: This woman's care was less than adequate because of misjudgments on the part of nurses and physicians—misjudgments based on arrogance and a lack of respect. Yet maintaining a strong doctor-patient relationship resulted in identifying and stopping illegal behavior rather than in a lawsuit against the hospital. Finally and most important, I am telling this story because of the letter that I subsequently received from this woman. I have—as I am sure all of you will in the future—received honors, awards, and certificates. None of these is on my wall. However, this letter is one that I did frame and hang. It reads:

> "Dear Dr. Stimmel: Just a note to say thank you for many things. First, for being the 'doc' that I have complete faith and trust in, in his treatment and diagnosis. Second, for always treating me as a human being, no matter what my financial situation was at that time. Third, for being there at all times and my knowing that you were just a telephone call away."

My one wish is that all of you will receive many such letters. This is really what medicine is all about.

As you will be doing today, those entering medicine take an oath of service. Thanks to the generosity of Dr. Gold, today's White Coat Ceremony is replicated across the country. This, of course, is wonderful. However, if there were to be only one required remembrance for a physician, I would ask you to recall the words written not by a physician but by a man who truly understood human behavior. These are the words spoken by Polonius to Laertes through the pen of William Shakespeare: "This above all, to thine own self be true, and it must follow, as the night the day, thou canst not then be false to any man (5)."

I would ask that you all be true to yourselves, taking pride in the knowledge that you will acquire in the next four years, while retaining the humility and empathy essential to being a physician.

Congratulations! You are embarking on a wonderful journey. I envy you.

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Combination Antiplatelet Agents in Ischemic Cerebrovascular Disease

Michael Moussouttas, M.D.[1], and Nikolaos Papamitsakis, M.D.[2]

Abstract

Combination antiplatelet agents with multiple mechanisms of action are being used with increasing frequency for vascular disorders, including cerebrovascular disease. Limited data exist regarding the efficacy of combination antiplatelet therapy in the primary or secondary prevention of cerebral ischemia, and combination therapies are often used without adequate evidence of efficacy. However, over the last few years, several cerebrovascular and cardiovascular trials have provided some preliminary information on the effectiveness of various combination therapies in preventing cerebral ischemic disease. This article reviews recently completed cerebrovascular and cardiovascular trials that tested a combination antiplatelet regimen against aspirin alone, and that assessed cerebral ischemia as an outcome measure. Controversies pertaining to these trials and to the use of the various combination antiplatelet regimens are discussed.

Based on cardiovascular studies, clopidogrel in combination with aspirin has not been proven superior to aspirin alone for the primary prevention of cerebral ischemia. No data exists regarding the combination of clopidogrel and aspirin for the secondary prevention of cerebrovascular disease. The combination of aspirin plus extended-release dipyridamole (xrDP) appears to be superior to aspirin alone in the secondary prevention of cerebral ischemia, but may compromise cardiovascular protection in patients with coexisting coronary artery disease. Combination therapy with aspirin and clopidogrel seems to increase the risk of major hemorrhages, whereas aspirin plus xrDP does not. Ongoing trials are expected to clarify the role of various combination antiplatelet regimens.

Key Words: Antiplatelet, combination therapy, cerebral, ischemia, infarction, vascular, aspirin, clopidogrel, dipyridamole, cerebrovascular.

Introduction

Since the establishment of aspirin as the first antiplatelet agent proven effective for the secondary prevention of ischemic cerebrovascular disease, newer antiplatelet agents with different mechanisms of action have been developed, in the hope of providing greater antithrombotic activity and greater protection against cerebral ischemia. However, no single antiplatelet agent has yet proven to be both safer and more effective than aspirin for cerebrovascular patients (1, 2). As a result, combination therapies aimed at inhibiting platelet function by multiple mechanisms are increasingly being considered and tested. Experimental animal models have demonstrated that the combinations of aspirin plus ticlopidine (3), and aspirin plus clopidogrel (4), are more potent than aspirin alone in preventing platelet aggregation. In a study on human plasma samples, the combination of aspirin and dipyridamole (DP) was found to reduce both the number and size of platelet aggregates in an additive fashion (5).

Currently available antiplatelet agents for use instead of aspirin or in combination with aspirin include the thienopyridines (ticlopidine and clopidogrel) and DP preparations (regular or extended release). Aspirin acts by irreversibly inhibiting intracellular platelet cyclooxygenase production of thromboxane A2 (TXA2), a potent pro-aggregant. The thienopyridines irreversibly block platelet membrane adenosine diphosphate (ADP) receptors, thereby preventing ligand-induced aggregation. DP reversibly inhibits intracellular platelet phosphodiesterase inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanine monophosphate (cGMP), two second messenger anti-aggregants, and prevents the uptake of adenosine by red cells and the vessel wall, leading to vasodilation (6). Whereas several recent major trials have demonstrated the relative efficacy of these agents individually against placebo or aspirin (7–9), only one modern study has compared combination antiplatelet therapy to aspirin in patients with cerebrovascular disease (10). However, antiplatelet drug combinations have also been

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[1]Cerebrovascular Division and [2]Cerebrovascular Program Director, Department of Neurology, Seton Hall University, South Orange, NJ.

Address all correspondence to Michael Moussouttas, M.D., Neuroscience Institute, JFK Medical Center, 65 James Street, Edison, NJ 08818; e-mail: arista1@pol.net

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tested in patients with cardiovascular disease, where cerebrovascular endpoints were included in the outcome assessment (11–13).

This article reviews and compares the data obtained from recent large, randomized cerebrovascular and cardiovascular trials that compared combination antiplatelet therapy to aspirin alone, and that assessed cerebral ischemia as a primary or secondary outcome measure. An overview of the study outcomes is provided in the accompanying table.

Review of Studies

The second European Stroke Prevention Study (ESPS-2) was the first modern trial to test combination antiplatelet treatment against aspirin in patients with cerebrovascular disease (10), and the only one to employ very-low-dose aspirin. More than 6,000 patients who had experienced a cerebral infarction (CI) or transient ischemic attack (TIA) within 3 months of enrollment were randomized to receive one of four treatments twice daily: aspirin 25 mg plus extended-release DP 200 mg (xrDP), aspirin 25 mg alone, xrDP 200 mg alone, or placebo. Outcome measures were determined at two years, and included TIA, CI, myocardial infarction (MI), vascular mortality (VM), and the composite outcome of CI/MI/VM. The combination of aspirin plus xrDP proved superior to aspirin alone for the CI and composite outcomes, but not for the TIA, MI, or VM outcomes. For the CI outcome, a 23% relative risk reduction was demonstrated for the aspirin/xrDP combination over aspirin alone, beyond the 18% relative risk reduction observed for aspirin vs. placebo. There was no increase in major hemorrhages, defined as any hemorrhage requiring transfusion, in the aspirin/xrDP group compared to aspirin alone.

In the Stent Anticoagulation Restenosis Study (STARS) (11), 1,965 patients undergoing coronary artery stenting were randomized to one of three different antithrombotic regimens—aspirin 325 mg daily, aspirin plus ticlopidine 250 mg twice a day, or aspirin plus warfarin for an INR of 2–2.5. The main endpoints of this trial consisted of clinical and angiographic cardiac outcomes within 30 days of coronary stenting, and included MI and a composite outcome of MI, VM, vessel rethrombosis, and need for revascularization. In this trial, the combination of aspirin plus ticlopidine was more effective than aspirin alone or aspirin plus warfarin for the MI and composite outcomes, but resulted in more major hemorrhages, defined as any hemorrhage requiring transfusion. Unfortunately, the total number of events in each group was too small to draw firm conclusions from, and the short duration of this trial limited its overall usefulness with regard to cerebrovascular outcomes.

The Clopidogrel in Unstable angina and Recurrent Events (CURE) study selected patients who presented within one day of non-Q wave myocardial ischemia (12), and randomized over 12,500 patients to daily aspirin 75–325 mg and placebo, or to daily aspirin 75–325 mg plus clopidogrel 300 mg once followed by clopidogrel 75 mg daily. Main outcome measures at 1 year included MI, CI, and VM, individually and as a composite outcome. The combination of aspirin and clopidogrel proved to be superior to aspirin alone for the MI and composite outcomes, but not for the CI or VM outcomes. Major hemorrhages, defined as any hemorrhage requiring transfusion of two or more units of red cells, were more frequent in the aspirin/clopidogrel group. When

TABLE

Vascular Outcomes from the Various Combination Antiplatelet Trials.

	ESPS-2	STARS	CURE	CREDO
Cerebral Infarction	−23% (0.006)	NR (NS)	−14% (NS)	−25% (NS)
Myocardial Infarction	−10% (NS)	−80% (0.014)	−23% (SS)	−22% (NS)
Vascular Mortality	−3% (NS)	NR (NS)	−7% (NS)	−25% (NS)
CI / MI / VM	−22% (<0.01)	−85% (<0.001)†	−20% (<0.001)	−27% (SS)
Major Hemorrhage	NR (NS)	+306% (0.002)	+38% (0.001)	+31% (0.07)

All values pertain to combination antiplatelet therapy vs. aspirin alone. Values indicate relative risk as percentages (p-values in parentheses).

CI = cerebral infarction, MI = myocardial infarction, VM = vascular mortality.

ESPS-2 = European Stroke Prevention Study 2, STARS = Stent Anticoagulation Restenosis Study, CURE = Clopidogrel in Unstable angina and Recurrent Events, CREDO = Clopidogrel for the Reduction of Events During Observation.

NR = not reported, NS = not significant, SS = statistically significant.

†Combined outcome of MI, mortality, rethrombosis, and need for revascularization.

major hemorrhages and the composite outcome were merged as a single endpoint, the overall relative risk reduction for aspirin/clopidogrel vs. aspirin decreased from 18% to 8%. Only about 4% (n=500) of the patients enrolled in this study had a history of CI, and no data was available regarding outcome measures in this population.

In the Clopidogrel for the Reduction of Events During Observation (CREDO) study (13), 2,116 patients undergoing elective percutaneous coronary intervention (PCI) were randomized to receive either a clopidogrel 300 mg loading dose 3 – 24 hours prior to PCI followed by clopidogrel 75 mg daily for 1 year, or placebo prior to PCI followed by clopidogrel 75 mg daily for 4 weeks and then placebo again. All patients received 325 mg of aspirin from 3 – 24 hours before to 4 weeks after PCI, and then 81 – 325 mg each day thereafter. The main outcome measure at 1 year was the composite of MI, CI, and mortality, and these endpoints were also assessed individually. The treatment group receiving a clopidogrel load followed by daily clopidogrel for 1 year experienced a significant reduction in the combined outcome, but did not show a significant advantage regarding the individual outcomes of MI, CI, or mortality. A trend towards more major hemorrhages, defined as intracranial hemorrhage or a decrease in hemoglobin by 5 g/dL, was observed in the group continuously receiving clopidogrel ($p=0.07$). Fewer than 7% (n=141) of patients enrolled in this study had a history of previous CI.

Discussion

The results of the above studies suggest that the combination of aspirin plus a thienopyridine is superior to aspirin alone in preventing recurrent myocardial ischemia in patients presenting with acute coronary syndromes and in those requiring coronary artery stenting. However, in no study was aspirin plus a thienopyridine shown to be better than aspirin alone in preventing cerebral ischemic events. Conversely, in patients presenting with a cerebrovascular event, the combination of aspirin plus xrDP appeared to be twice as effective as aspirin alone in preventing recurrent cerebral ischemia, but was not shown to be superior to aspirin in preventing myocardial ischemia. All combination therapies displayed an advantage over aspirin alone in the composite outcome of CI/MI/VM, owing mostly to the dominant effect on their respective primary endpoint of MI or CI, but no combination influenced overall mortality. Finally, when compared to aspirin alone, the combination of aspirin plus a thienopyridine seemed to result in more major hemorrhagic complications, whereas aspirin plus xrDP did not.

Concordant with the results of the combination antiplatelet studies, a differential effect among single antiplatelet agents for different types of vascular disease has also been suggested in previous clinical trials and meta-analyses (9, 14). Epidemiological data has indicated that patients presenting with myocardial ischemia are more likely to experience and die from a recurrent cardiovascular event, whereas patients presenting with cerebral ischemia are more likely to experience and die from a recurrent cerebrovascular event (15, 16). Therefore, the type of clinically manifest vascular disease may not only predict the future vascular risk, but may also dictate a specific preventive antiplatelet treatment (17).

The difference in study populations among the combination antiplatelet trials, however, represents an important limitation to the direct comparison of study outcome results. Whereas ESPS-2 included patients who had experienced a cerebral ischemic event, CURE and CREDO selected patients with active or latent coronary artery disease. Therefore, with regard to ischemic cerebrovascular disease, ESPS-2 was the only study of secondary prevention, whereas CURE and CREDO were essentially primary prevention studies. Interestingly, the findings from these three combination antiplatelet studies mirror those testing the efficacy of aspirin alone, in which a benefit was shown for secondary prevention but not for the primary prevention of cerebral ischemia (18). Thus, the failure of aspirin/clopidogrel to prevent a first cerebral ischemic event may simply reflect the ineffectiveness of antiplatelet agents in general for the primary prevention of ischemic cerebrovascular disease. Alternatively, greater numbers of patients may have been needed in these studies to detect a small but relevant advantage.

Controversies

Controversy abounds regarding the most effective antiplatelet regimen available for the prevention of noncardiogenic cerebral ischemia (19). With the introduction of combination antiplatelet agents, this debate has only intensified and become more complex. Due to severe unfavorable hematologic side effects, ticlopidine alone or in combination with aspirin is now rarely used for antithrombosis in either cardiac or cerebral vascular disease (2). Consequently, with regard to combination therapy, there are currently two options frequently selected in clinical practice—aspirin plus clopidogrel or aspirin plus xrDP.

Aspirin plus xrDP

Critics of the aspirin/xrDP combination have challenged the validity of ESPS-2 in view of prior aspirin/DP studies that failed to show a benefit over aspirin alone in the secondary prevention of cerebral ischemia (20–23). However, direct comparisons between the newer and older studies are impeded by the fact that prior studies were much smaller in size, used lower total daily doses of DP, and employed regular DP instead of the extended-release form (14, 21–23). Concern has also been voiced about determining treatment efficacy based on a single positive trial (20), yet ticlopidine and clopidogrel were also tested only once against aspirin in patients with cerebrovascular disease (8, 9), and have received general acceptance for this indication (17).

Investigational "misconduct" at one participating center raised concerns about the validity of the ESPS-2 results (24), but all data procured from the offending center was reportedly excluded from the final analysis. The use of a placebo arm at a time when aspirin had already been proven effective raised ethical concerns about the design of this trial (25), yet proponents claim that such a design validated the efficacy of low-dose aspirin, proved the efficacy of xrDP, and demonstrated the additive effects of combining antiplatelet agents (10).

Other issues raised have included the tolerability and cost effectiveness of aspirin/xrDP. In ESPS-2, 38% of patients taking aspirin/xrDP developed cephalgias, and 8% discontinued treatment for this reason (10). Despite evidence suggesting the rapid development of tolerance to this side effect, at least 3% of patients may ultimately be unable to continue taking aspirin/xrDP (26). Some practitioners have preferred using daily aspirin in combination with the less expensive immediate-release form of DP given four times a day, since generic xrDP is currently unavailable in the United States. However, this combination has not been proven superior to aspirin alone, immediate-release DP is associated with less bioavailability than the extended-release preparation (27), and patient compliance may be expected to decline with the more frequent dosing required. In one report, the combination of aspirin and xrDP was even found to be more cost effective in cerebrovascular prophylaxis than aspirin alone (28).

The very low dose of aspirin used for comparison against combination therapy in ESPS-2 has raised questions as to the validity of the results, since most antiplatelet trials have routinely employed control doses of at least 75 mg (8, 9, 11–13). Prospective randomized trials and meta-analyses, however, have shown no difference in efficacy for aspirin doses as low as 30 mg per day (29, 30). Insufficient cardioprotection by the very low aspirin dose used in the aspirin/xrDP formula for patients with concurrent cardiovascular disease has also been a major issue of contention, and has limited the generalized application of aspirin/xrDP for patients with cerebral ischemic disease (see discussion below).

Aspirin plus Clopidogrel

Arguments against the use of aspirin plus clopidogrel have included the absence of a study primarily directed towards patients with cerebrovascular disease, the lack of an effect on cerebral ischemia in patients with cardiovascular disease, and the increased risk of severe hemorrhagic complications (31). Proponents of the use of aspirin/clopidogrel have pointed to a trend towards efficacy for cerebrovascular outcomes, and have attributed the increased rate of major hemorrhages to aspirin doses exceeding 200 mg per day, to the concomitant use of heparin or fractionated heparin products, and to the arterial punctures and surgical procedures performed (CURE data) (32). However, no difference in average aspirin dose between the two treatment arms was reported, a similar percentage of patients in each treatment arm received heparin or fractionated heparin products, and fewer patients in the aspirin/clopidogrel group received GPIIb/IIIa or fibrinolytic therapies as a result of treatment efficacy (12). In addition, fewer invasive procedures were performed in the aspirin/clopidogrel group, also because of treatment efficacy, and the number of surgically unrelated major hemorrhages from aspirin/clopidogrel was still almost twice that of aspirin alone (12).

It has also been suggested that the risk of hemorrhage from aspirin/clopidogrel may be even greater for cerebrovascular patients than for cardiac patients, given the propensity for acute cerebral infarctions to undergo hemorrhagic transformation (31). However, whether any increase in cerebral hemorrhages will be clinically relevant or asymptomatic remains purely speculative.

Cerebrovascular Disease and Cardiovascular Disease

One of the most debated topics in the management of patients with cerebrovascular disease involves the choice of antiplatelet therapy for patients with coexisting cardiovascular disease. According to major studies, as many as 35% of patients presenting with cerebral ischemia have a history of coronary artery disease (10). This issue has recently taken on greater importance with the introduction and approval of antiplatelet agents containing low doses of aspirin for the secondary prevention of cerebrovascular disease. In randomized clinical trials and meta-analyses, aspirin doses as low as 30–50 mg/day have been shown to be effective for the secondary prevention of cerebral ischemia (10, 29, 30, 33). In contrast, aspirin doses of at least 75 mg/day are required for the primary or secondary prevention of myocardial ischemia (34, 35). For patients presenting with cerebral ischemia and a history of symptomatic coronary artery disease or an indication for the primary prevention of cardiovascular disease, no information exists regarding the optimal antithrombotic regimen. If aspirin/xrDP is to be used, the low daily dose of aspirin may compromise cardioprotection according to existing cardiac guidelines. Consideration may be given to adding extra aspirin, but the risk-benefit profile of this combination has never been tested in cerebral or cardiac vascular disease. Studies comparing low aspirin doses (<75 mg) to conventional doses in patients with coronary artery disease may be needed to resolve this issue.

For patients with acute coronary syndromes and for those undergoing percutaneous coronary interventions, daily aspirin plus clopidogrel is the indicated antiplatelet treatment (35). However, whether this regimen maintains or compromises cerebrovascular protection in patients with a history of cerebral ischemia remains uncertain. Additionally, the optimum duration of this treatment has yet to be defined (35), and the issue of whether and when to substitute another antiplatelet regimen also remains unresolved.

Adverse Drug Effects and Interactions

In addition to the commonly cited hemorrhagic and gastrointestinal complications from antiplatelet agents, several pertinent adverse effects and drug interactions from the constituent compounds of these combination therapies have been reported. Potential adverse effects from DP have included aggravation of angina in patients with severe or active coronary disease (36), exacerbation of hypotension (37), precipitation of TIAs in patients with cerebral hemodynamic insufficiency (38), and decreased potency of acetylcholinesterase inhibitors used for dementia (37). Conversely, an advantageous antihypertensive effect by DP has been suggested (39), but clinically disproved (40), and in one study the combination of DP plus aspirin was found to be significantly more cardioprotective than aspirin alone (41).

Immune-mediated thrombocytopenia represents a serious but very rare potential complication of clopidogrel use, with a total of eleven cases and one fatality reported (42). Laboratory experiments have demonstrated a reduction in platelet inhibition from the coadministration of clopidogrel and lipophilic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors such as atorvastatin (43, 44), yet no adverse effects from this combination have been observed in clinical practice (45).

The decreased efficacy of angiotensin-converting enzyme (ACE) inhibitors and the increased efficacy of oral antihyperglycemic agents with aspirin is well known (46). Finally, aspirin resistance with decreased antiplatelet activity and thus inadequate cerebrovascular protection is an increasingly recognized consequence of aspirin use, particularly with low doses and coated preparations (47).

Conclusions

To date, no antiplatelet regimen has been proven effective in the primary prevention of ischemic cerebrovascular disease. The combination of aspirin and clopidogrel is of unproven benefit for preventing cerebral ischemia in patients with coronary artery disease (primary prevention), and may carry an increased risk of major hemorrhage. There is no data available regarding the use of this combination in the secondary prevention of cerebral ischemia. Consequently, it has been suggested that only those cerebrovascular patients with active coronary artery disease and a low risk of hemorrhage be considered for treatment using aspirin and clopidogrel (31).

The combination of aspirin and xrDP appears to be more effective than aspirin alone in preventing recurrent cerebral ischemic events (secondary prevention), and may not increase the risk of major hemorrhage. However, the combination of aspirin and xrDP is of uncertain benefit in patients with an indication for the primary or secondary prevention of coronary artery disease, and may even be detrimental, given the low dose of aspirin contained.

Future therapeutic strategies for the prevention of ischemic cerebrovascular disease may increasingly employ not only combination antithrombotic agents, but also combination treatments with antihypertensive agents, “statins,” and vitamins (48).

Ongoing Trials

The MATCH study compared the combination of aspirin 75 mg plus clopidogrel 75 mg against clopidogrel 75 mg alone in 7,599 patients presenting within 3 months of a cerebral ischemic event, and possessing one other vascular risk factor. Other vascular risk factors included prior CI, MI, angina pectoris, symptomatic peripheral artery disease, or diabetes. Outcomes included a composite of CI/MI/VM, as well as the individual endpoints of CI, MI and hemorrhage, assessed at 18 months. The recently announced results (unpublished data) have indicated no benefit from combination therapy over clopidogrel alone, and more severe hemorrhages from aspirin plus clopidogrel (49). Unfortunately, by not having an aspirin arm for comparison, it is difficult to draw conclusions regarding the relative efficacy of combination aspirin plus clopidogrel therapy versus any of the other available antiplatelet regimens, based on this study (1).

Ongoing secondary prevention trials comparing aspirin plus clopidogrel to aspirin alone include the SPS3 study of patients presenting with lacunar infarctions, the CARESS study of patients with recently symptomatic ≥ 50% carotid stenosis, the FASTER study of patients with acute (< 12 hours) cerebral ischemia, and the CHARISMA study of patients with multiple vascular risk factors and various types of vascular disease. Primary outcomes in SPS3 will include recurrent infarction, magnetic resonance imaging measures of subcortical ischemic changes, and vascular impairment in intellect. The main endpoints in the CARESS study will be based on transcranial ultrasound measurements of microembolic signals in the ipsilateral middle cerebral artery, as well as platelet aggregation analyses. For FASTER, endpoints will include CI and MI/CI/VM, whereas in CHARISMA the primary outcome will simply be the composite of MI/CI/VM.

Other combination antiplatelet trials underway include the ACTIVE study of aspirin plus clopidogrel vs. warfarin or aspirin alone in patients with atrial fibrillation, and the ARCH study of aspirin plus clopidogrel vs. warfarin in patients with complex aortic atheroma. The ESPRIT study will compare the relative efficacy of aspirin, aspirin plus DP, and warfarin, in patients presenting with a cerebral ischemic event, and in what will be the largest cerebrovascular prevention trial ever conducted, and the first to compare two non-aspirin antiplatelet agents, the PROFESS study will compare aspirin plus xrDP against clopidogrel alone.

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Complete Remissions in Chemotherapy of Lung Cancer Models Induced in Mice by Asbestos

William E. Smith, M.D.[1][†], Doras D. Hubert, B.A.[1], Ebrahim Yazdi, B. Pharm.[1], Stephen M. Holiat, D.V.M.[1],
Elizabeth Cutler Bissell, B.A.[1], Laurel Melcher Watts, B.A.[1], Raymond A. Baylouny, Ph.D.[2],
and Harold J. Sobel, M.D.[3]

Abstract

Chemotherapy trials were run with mice bearing transplants of carcinomas originally induced from fetal mouse lung cells by asbestos. After treatments with a nitrosourea (PCNU)*, mice bearing transplants of a large-cell carcinoma (ASB XIV) had complete remissions (CR) in 13 of 20 animals on a 15 mg/kg regimen, in 6 of 20 on an 8 mg/kg regimen, and in none of 10 on a 4 mg/kg regimen. With comparable total doses, treatment was most effective when PCNU was given in a few large doses. In groups where CRs occurred, continued PCNU treatment of animals without CRs prolonged survival but yielded no additional CRs. No CRs of ASB XIV occurred in 80 mice treated with eight other anticancer agents or in 50 controls injected with 0.9% NaCl solution.

In mice bearing transplants of a squamous cell carcinoma (ASB XIII), treatments with PCNU were followed by CRs in 3 of 38 animals on 15 mg/kg regimens and in 3 of 28 animals on 8 mg/kg regimens. In groups of 6 mice fed a retinoid (Ro 10-9359) and treated with PCNU, CRs of ASB XIII occurred in 3 animals in each of two trials and in none in a third trial. Ro 10-9359 inhibited growth of transplants of squamous cell carcinoma LC 12 that had been induced from fetal mouse lung cells by a polycyclic hydrocarbon.

In trials of four other anticancer agents vs. ASB XIII, CRs occurred only with cyclophosphamide (CPA). There were 7 CRs among 8 mice treated with CPA 100 mg/kg × 3, no CRs in 10 after 100 mg/kg × 2, one CR in 8 after 50 mg/kg × 3, and no CRs in 6 after 50 mg/kg × 4. With the 50 mg/kg × 4 regimen of CPA and 7.5 mg/kg PCNU on the same days, there were 5 CRs in 8 mice. As a single agent, aziridinylbenzoquinone (AZQ) increased life span but gave no CRs. There were CRs of ASB XIII in all of 8 mice after toxic combined therapy with PCNU and AZQ. There were no CRs in 66 control mice bearing ASB XIII.

Key Words: Lung cancer, nitrosourea, retinoids, asbestos cancer.

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*1-(2-chloroethyl)-3-(2,6-dioxo-piperidyl)-1-nitrosourea

Background

In the 1960s, Dr. Irving J. Selikoff saw patients with lung cancers or pleural mesotheliomas who had worked in a New Jersey factory handling asbestos. At that time, one of us (Dr. William Smith) had facilities for experimenting with animals at Fairleigh Dickinson University's Health Research Institute in Madison, New Jersey. The owner of the factory introduced Dr. Selikoff and Dr. Smith, gave them a sample of asbestos (amosite) used in his factory, and suggested they test whether it would induce tumors in animals. It did. Their report (1) provided some of the early evidence for carcinogenicity of asbestos.

Epidemiological studies by Dr. Selikoff and his group at Mount Sinai established carcinogenicity of asbestos for humans (2–3). Dr. Smith became an assistant clinical professor in Dr. Selikoff's group at Mount Sinai, and animal experiments with asbestos were continued by Dr. Smith and his colleagues at the Health Research Institute.

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[1] Retired, Health Research Institute and [2] Department of Chemistry, Fairleigh Dickinson University, Madison, NJ; and [3] University of Medicine and Dentistry of New Jersey, Newark, NJ.

[†] Deceased.

Address all correspondence to Mrs. Doras Hubert, 2 North Road, Glens Falls, NY 12801.

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Introduction

Tumors resembling human mesotheliomas were found in hamsters after a single intrapleural injection of the amosite or chrysotile varieties of asbestos (1). Incidence of such tumors was found to be related to size of fibers and dose (4 – 7). Chemotherapy trials were run with hamsters bearing transplants of an epithelial mesothelioma induced by asbestiform tremolite, a sarcomatous mesothelioma induced by chrysotile, and a mixed epithelial-sarcomatous mesothelioma induced by crocidolite. Partial responses (increased lifespan) but no complete remissions (CR) were achieved (8 – 10). Cryopreserved cells from these tumors, identified respectively as mesotheliomas 10 – 24, H 12 and H 75, are available from Tumor Bank, National Cancer Institute, Bethesda, MD.

Since inhalation exposures of experimental animals require elaborate equipment and intratracheal injections are difficult to perform, we used the "tissue transplant technique" for experiments with mice (11). By this technique minced lungs from near-term BALB/c mouse fetuses are mixed with a material to be tested for carcinogenicity and implanted by trocar through skin slits into posterior thigh muscles of young adult mice of the same strain. Implants of minced fetal mouse lungs produce growths of alveolar lung tissue and bronchiolar-like structures. When these implants are made with polycyclic hydrocarbon carcinogens there is adenomatoid change, adenocarcinomas, squamous metaplasia and squamous cell carcinomas (12). The "tissue transplant technique" was used for tests for inhibition of carcinogenesis by vitamin A. A diet high in vitamin A increased, rather than decreased, induction of cancers from fetal mouse lung tissue by methylcholanthrene, a polycyclic hydrocarbon carcinogen (13).

This technique was also used to test for the carcinogenicity of various preparations of asbestos. At 27 sites where implants of fetal mouse lung tissue were made together with a preparation of harsh chrysotile asbestos, there was fibrosis, adenomatoid change and squamous metaplasia. At 9 of these sites, there were lesions with gross and histologic characteristics of neoplasia: 4 epidermoid carcinomas, 2 adenocarcinomas and 3 sarcomas (14). The sarcomas may have arisen from tissues of the new hosts rather than from cells in the implants. Two of the carcinomas were maintained in serial generations by transplants into thigh muscles of new hosts for chemotherapy trials.

The preparation of asbestos used with these implants was a harsh chrysotile with a broad range of fiber sizes. Average fiber length was 36 microns, as measured at 100 (by optical microscopy (15). When this preparation was milled to reduce the length of most fibers to below 5 microns, it did not induce carcinomas from the implants of fetal mouse lung cells (16). And no carcinomas arose from such implants made with long-fiber preparations of other varieties of asbestos: soft chrysotile, International Union Against Cancer (UICC) Standard Reference Samples of crocidolite, amosite and anthophyllite (16). Histologic sections show that the samples that did not induce carcinomas in these experiments caused little fibrosis at the intramuscular sites in mice, in contrast to the extensive fibrosis that surrounded implants made with the long-fiber preparation of harsh chrysotile. This is evidence that carcinogenicity of asbestos is related to its fibrogenicity.

The UICC Standard Reference Samples and samples of soft chrysotile were found by others to induce carcinomas of the lungs and pleural mesotheliomas after inhalation exposures of rats (17). Other inhalation experiments with chrysotile, amosite and crocidolite found that these induced lung tumors in rats but not in rabbits, guinea pigs or gerbils (18). Papillary bronchial carcinomas developed in two mice in those experiments, but a similar tumor was found in a control mouse that had not been exposed to asbestos. That humans are a susceptible species is shown by epidemiological studies associating exposure to asbestos with carcinomas of lungs and mesotheliomas in humans (3).

Except for the work reported in references 11 and 12, all of the above experiments by our group were carried out at Fairleigh Dickinson University's Health Research Institute in Madison, New Jersey, which closed in 1983. Some results of our chemotherapy trials with mice were briefly reported (19 – 21). As treatment of lung cancers remains a challenging subject, the above trials and previously unreported trials are detailed in the present paper.

Materials and Methods

Animals from a breeding colony of BALB/c mice, maintained in our laboratory, were fed Purina Mouse Chow #5015 and water ad libitum. For serial passage for chemotherapy trials, we used two lines of carcinomas that had been induced from fetal mouse lung cells by the above-described preparation of long-fiber, harsh chrysotile (14). Tumors were removed aseptically. Living tissue was selected and minced with scalpels. Approximately 2 mm^3 of the mince was transplanted by trocar through skin slits wiped with an antiseptic (Betadine) into right posterior thigh muscles of young adult BALB/c males.

Body weights of animals were recorded at the time of transplant and at weekly intervals thereafter. Treatments were started on Day 7 after transplant. Control animals received intraperitoneal (ip) injections of sterile 0.9% NaCl solution on the same schedule as that of the most extensively treated group in each experiment. Dosage of drugs included LD_{10} values for mice (22). Drugs were supplied by the Drug Evaluation Branch, National Cancer Institute, Bethesda, MD, and were:

- NSC-95466 — PCNU: [1-(2-chloroethyl)-3-(2,6-dioxo-piperidyl)-1-nitrosourea]
- NSC-301739 — dianhydroanthracenedione dihydrochloride
- NCS-119875 — cis-DDPt [cis-diamine-dichloroplatinum]
- NSC-139105 — triazinate
- NSC-132313 — dianhydrogalactitol
- NSC-182986 — AZQ: [aziridinylbenzoquinone]
- NSC-259272 — ara-A-5′-phosphate
- For use with ara-A-5′-phosphate, an adenosine deaminase inhibitor (pentostatin) was provided by Parke, Davis and Company, Detroit, MI.
- Other drugs utilized were: cyclophosphamide (Cytoxan [CPA]), Mead Johnson Laboratories, Evansville, IN.; doxorubicin HCl (Adriamycin), Adria Laboratories, Inc., Wilmington, DE; and 5-fluorouracil and retinoids, Hoffman-La Roche, Inc., Nutley, NJ.

Sizes of tumors at implant sites in test and control animals were measured with calipers and compared at Day 28 after transplant. Percent inhibition of tumor size (ITS%) was calculated for a treated group and its control group by the following formula:

$$\frac{\text{Average controls} - \text{Average treated}}{\text{Average Controls}} \times 100$$

The number of days that each animal lived was recorded. Average survival of mice in a treated group was compared with average survival of its control group, and any increased lifespan (ILS%) was calculated. In a group where complete remissions occurred, usually by 28 days, ITS% was calculated for all animals in that group but ILS% was calculated only for those without remissions. Except where stated, each experiment consisted of a control group and 2–6 treatment groups, with 10 or 6 male mice per group. All animals were examined by necropsy with special attention to presence or absence of metastases. Tissues from representative lesions were fixed in 10% neutral buffered formalin. Sections were stained with hematoxylin and eosin.

Results

Transplants of each of the 2 tumor lines, identified as ASB XIII and ASB XIV, resulted in progressive growths in essentially all new hosts, leading to death of controls within about 2 or 3 months, with large tumors at the sites of transplantation. The line designated as ASB XIII was a squamous cell carcinoma (Fig. 1). It was locally invasive, but no metastases were found. The line designated ASB XIV was a large cell carcinoma (Fig. 2). It metastasized widely, notably to the lungs (Fig. 3).

Doses and regimens of tested drugs are detailed in tables, which show inhibition of tumor size (ITS) at Day 28 after transplant, any increase in lifespan (ILS) of treated animals, and any complete remissions (CRs).

Data from trials with ASB XIV (10 animals in each group) are presented in Table 1, from which it can be seen that in 5 control groups all hosts died between 34 and 59 days (average: 43 days). All of these 50 control animals had large tumors at their transplant sites. Numerous metastases were found in lungs of the control hosts that lived more than 6 weeks after transplant.

As shown in groups of 10 animals (Table 1) and briefly reported (19), best results with ASB XIV followed treatments with PCNU. CRs occurred in 2 of 10 animals after 8 mg/kg 1 × q week × 3, in 4 of 10 animals after 8 mg/kg 1 × q week × 5. The other 14

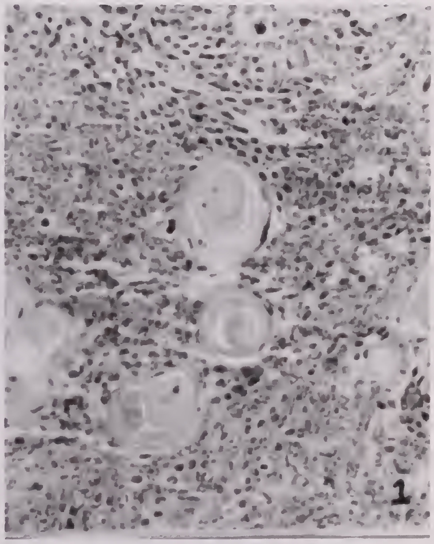

Fig. 1. Section of ASB XIII tumor growing in thigh muscles of a mouse of the 128th transplant generation. This tumor was removed 50 days after transplant. It was a 30 mm spherical mass with moist keratin in center and rugose firm tissue around periphery. It is a squamous cell carcinoma. Note prominent "pearl" formation. (Hematoxylin and eosin × 288.)

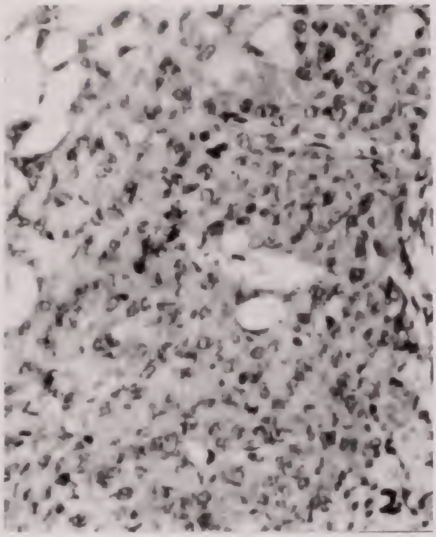

Fig. 2. Section of ASB XIV tumor growing in thigh muscles of a mouse of the 170th transplant generation. This tumor was removed 43 days after transplant. It was a 20 mm spherical mass with necrotic center and soft living tissue around periphery. It is a large cell carcinoma with prominent mitotic activity. (H & E × 384.)

animals in these two groups continued on treatments with PCNU 8 mg/kg 1 × q week up to a total of 112 mg/kg. Their survival was prolonged, but all of these 14 mice developed progressively growing cancers that proved fatal.

A group of 10 animals was treated with 15 mg/kg of PCNU on Days 7 and 14. All of these animals had palpable tumors 4–9 mm in diameter when examined at Day 14. Seven of these animals had no palpable tumors when examined at Day 28 or subsequently. These 7 survived until Day 160, when they were sacrificed and examined by necropsy. No living tumors were found at their transplant sites; no metastases were found. These 7 are regarded as cures. They and similar animals are listed in the tables as complete remissions.

The other 3 animals in this group had palpable tumors on Day 28 and were continued on weekly doses of 15 mg/kg PCNU until they died. Two of these animals developed progressively growing tumors and died on Day 89, one with multiple metastases in the lungs, the other with no metastases. The tumor in the third animal regressed and was no longer palpable at Day 92, but recurred thereafter despite continued treatment to a total of 275 mg/kg. This animal died on Day 139 with a large tumor at the transplant site but no metastases.

In another trial, 10 animals were treated with 15 mg/kg of PCNU on Days 7, 14, and 21. All had palpable tumors 4–9 mm in diameter on Day 14. No tumors were palpable in any of these animals on Day

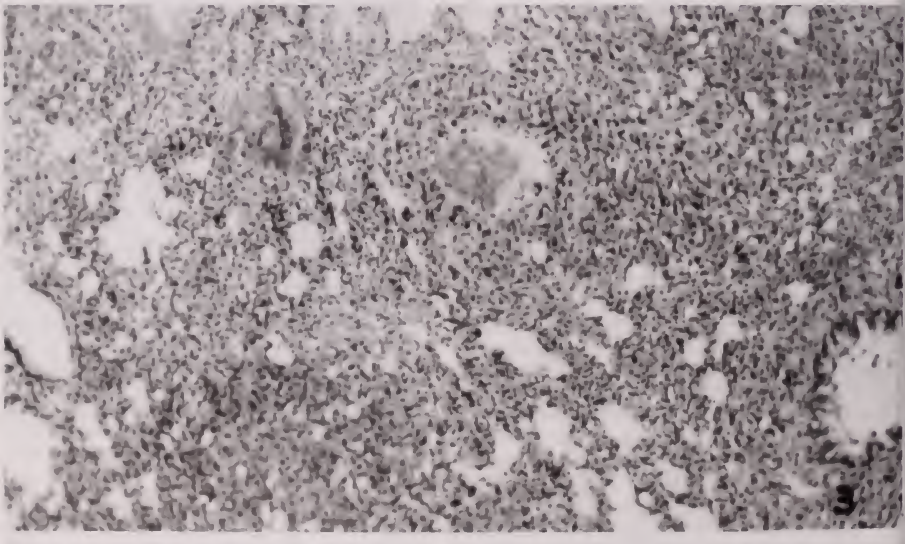

Fig. 3. Section of lung from mouse bearing tumor shown in Fig. 2. All lobes of the lungs were largely replaced by metastases. (H & E × 144.)

TABLE 1
Trials with Large Cell Carcinoma ASB XIV
10 Male Mice per Group

Dose mg/kg	**Total dose mg/kg**	**Treatment (days)**	**Average tumor size at day 28 mm**	**ITS[c] (%)**	**Survival after transplants[a] Average (days)**	**Range (days)**	**ILS[b] (%)**	**Complete remissions**
PCNU [1-(2-chloroethyl)-3-(2,6-dioxo-piperidyl)-1-nitrosourea]								
4	36	7–15	11	47	47	36–56	18	
8[d]	40	7,14,21,28,35	3	82	93	86–98	116	4
8[d]	24	7,14,21	7	58	70	58–101	63	2
15[d]	45	7,14,21	0	100	60	38–84	40	6
15[d]	30	7,14	1	94	89	89	106	7
dianhydroanthracenedione dihydrochloride								
1.5	9	7,11,14,18,21,25	16	–14	39	35–50	–10	
cis-diaminedichloroplatinum (cis-DDPt)								
6	18	7,11,14			20	9–44	–54	
3.33	16.65	7–11	15	–4	46	38–51	2	
triazinate								
51.3	461.7	7–11 + 14–17	13	11	44	15–66	–1	
dianhydrogalactitol								
4.75	23.75	7–11	15	–4	43	35–49	–5	
ara-A-5′-phosphate								
200	1800	7–11 + 14–17 together with pentostatin						
0.25	2.25	7–11 + 14–17	15	–9	41	21–50	–8	
pentostatin								
0.25	2.25	7–11 + 14–17	13	8	48	43–55	7	
doxorubicin HCl								
2	14	8,15,22,24, 30,36,43	15	9	52	43–60	10	
3	33	2 × q week	8	38	67	58–75	43	
5-fluorouracil								
50	550	2 × q week	13	19	50	37–64	16	
cyclophosphamide								
200	200	7 followed by						
25	225	2 × q week	16	1	45	35–53	6	
100	200	7,11 followed by						
25	250	2 × q week	16	1	44	42–46	5	
50	200	7,8,10,11 followed by						
25	200	2 × q week	17	–6	42	36–53	1	
saline controls								
		(5 groups)	16		43	34–59		

[a] Where complete remissions occurred, range, average survival and ILS refer to other animals in group.
[b] ILS = increase in lifespan.
[c] ITS = inhibition of tumor size.
[d] Animals without remissions at day 28 were continued on stated dosage. They had increased lifespan but no remissions.

28. There was one non-cancer-related death on Day 38. Another died of diarrhea on Day 43. Two developed progressively growing tumors and died with pulmonary metastases, on Days 75 and 84, despite continued weekly doses of 15 mg/kg of PCNU. The other 6 animals received no further treatments after Day 21. Those 6 animals remained free of palpable tumors and survived until Day 160, when they were sacrificed for examination. Necropsies revealed no living tumors at transplant sites. There was no evidence of metastases.

As shown in Table 1, there were no complete remissions of ASB XIV after a total dose of 36 mg/kg PCNU delivered in doses of 4 mg/kg, whereas CRs occurred after a total dose of 24 or 30 mg/kg delivered in doses of 8 or 15 mg/kg.

In all above-cited trials with PCNU, necropsies of animals revealed no gross lesions attributable to toxicity of PCNU. Histologic or biochemical studies for evidence of toxic effects were not made. Changes in average body weights of animals in trials with PCNU were not greater than in controls.

Trials of other drugs versus ASB XIV, also detailed in Table 1, achieved no CRs. Treatments with doxorubicin at 2 mg/kg to a total of 14 mg/kg gave 10% ILS. At 3 mg/kg to a total of 33 mg/kg, there was 43% ILS ($p<0.001$). In a trial with 5-fluorouracil at 50 mg/kg to a total of 550 mg/kg, there was 42% ITS but only 16% ILS. Three regimens of cyclophosphamide had no notable effect on tumor sizes at Day 28 or on survival times. Nor were there notable effects of tested regimens of dianhydroanthracenedione dihydrochloride, triazinate, dianhydrogalactitol, or ara-A-5′-phosphate with pentostatin or pentostatin alone.

No therapeutic responses were seen in animal treated with a tested dosage of cis-diaminedichloro platinum (cis-DDPt) (3.33 mg/kg daily to a total o 16.65 mg/kg). That group showed 15% loss in average body weight on Day 28. Administration of cis DDPt at doses of 6 mg/kg on Days 7, 11 and 1 proved toxic: 26% weight loss by Day 14 and deat before controls.

Trials with single agents for treatment of host bearing squamous cell carcinoma ASB XIII an treated with various drugs in groups of 10 male mic each are detailed in Table 2. Treatments were starte Day 7 after transplant. PCNU 8 mg/kg 1 × q wk × gave 25% ITS and 19% ILS. With 15 mg/kg PCN 1 × q wk × 7 ITS was 49% and there was one CR ILS was 33% for the other animals in this group.

After treatment with CPA 100 mg/kg on Days 7 an 11, there was 85% ITS but only 17% ILS and no CRs.

In dosage used for ASB XIV, there was no response of ASB XIII to doxorubicin or ara-A-5′ phosphate. There were no CRs in 20 controls.

Trials of combined therapies for squamous cel carcinoma ASB XIII are shown in Table 3, in whic

TABLE 2

Single Agent Trials with Squamous Cell Carcinoma ASB XIII
10 Male Mice per Group

Dose mg/kg	Total dose mg/kg	Treatment[a] (days)	Average tumor size at day 28 mm	ITS[d] (%)	Survival after transplants[b] Average (days)	Range (days)	ILS[c] (%)	Complete remissions
PCNU [1-(2-chloroethyl)-3-(2,6-dioxo-piperidyl)-1-nitrosourea]								
15	105	1 × q wk – 7	9	49	76	56–90	33	1
8	56	1 × q wk – 7	13	25	68	52–82	19	
cyclophosphamide (im)								
100	200	7,11						
	followed by:							
25	150	2 × q wk	2	85	75	60–89	17	
doxorubicin HCl (im)								
3	21	2 × q wk	14	9	53.1	37–62	–17	
ara-A-5′-phosphate								
200	2000							
	together with pentostatin							
0.25	2.5	QID × 7–11 + 14–18	15	3	69	57–83	8	
pentostatin								
0.25	2.5	QID × 7–11 + 14–18	17	–6	56	39–92	–13	
saline controls								
		(2 groups)	17	0	60	48–85		

[a] Treatments were started day 7 after transplant.
[b] Where complete remissions occurred, range, average survival and ILS refer to other animals in group.
[c] ILS = increase in lifespan.
[d] ITS = inhibition of tumor size.

TABLE 3

Combined Therapies with Squamous Cell Carcinoma ASB XIII
Six Male Mice per Group

Trial	Treatment[a]	Average tumor size at day 28		Survival after transplants[b]			Complete remissions
		mm	ITS[d] (%)	Average (days)	Range (days)	ILS[c] (%)	
CM 31							
#1	PCNU 15 mg/kg	2	86	43	41–44	−37	
#2	PCNU 8 mg/kg	8	43	74	58–85	25	
#3	PCNU 15 mg/kg Ro 10-9359	3	79	83	70–103	41	3
#4	PCNU 8 mg/kg Ro 10-9359	3	79	75	62–82	27	3
#5	Ro 10-9359	17	−21	47	40–68	−20	
#6	PCNU 15 mg/kg Ro 1-5488	3	79	83	70–97	41	1
#7	Ro 1-5488	14	0	51	37–71	−14	
#8	saline placebo	14		59	35–89		
CM 37							
#1	PCNU 8 mg/kg	10	41	83	64–100	50	1
#2	PCNU 8 mg/kg Ro 1-5488	11	35	70	36–79	21	
#3	Ro 1-5488	11	35	65	56–82	18	
#4	PCNU 8 mg/kg Ro 10-9359	8	53	47	18–77	−15	
#5	Ro 10-9359	15	12	50	39–56	−9	
#6	CPA 50 mg/kg	12	29	55	47–75	0	
#7	CPA 50 mg/kg Ro 10-9359	6	65	44	27–84	−20	1
#8	CPA 50 mg/kg Ro 1-5488	12	29	63	51–75	15	
#9	saline control	17		44	37–51		
#10	saline/placebo control	17		55[e]	40–70		
CM 33		**Eight Female Mice per Group**					
#1	PCNU 15 mg/kg	6	43	78	59–99	63	1
#2	PCNU 15 mg/kg CPA 100 mg/kg	0	100	76	66–84	58	4
#3	CPA 100 mg/kg	1	100	97	97	100	7
#4	AZQ 9 mg/kg	12	25	64	52–82	33	
#5	PCNU 15 mg/kg AZQ 9 mg/kg	0	100	33	13–104	−31	8
#6	saline control	17		4	35–76		
CM 36		**Eight Female Mice per Group**					
#1	PCNU 15 mg/kg	2	88	58	24–11	4	
#2	PCNU 15 mg/kg CPA 50 mg/kg	2	88	69	26–111	25	
#3	CPA 50 mg/kg	10	3	59	49–76	5	1
#4	PCNU 7.5 mg/kg CPA 50 mg/kg	2	88	87	79–97	55	5
#5	saline control	16		56	41–86		

[a] PCNU was injected ip on Days 7, 14, 21, 28 in CM 31 and CM 37, and on Days 7, 14, 21 in CM 33 and CM 36. Other drugs were injected subcutaneously or im on same days: Ro 10-9359 or Ro 1-5488 were added to food to provide 10 mg/kg daily on Days 2 to 28.

[b] Where complete remissions occurred, range, average survival and ILS refer to other animals in group.

[c] ILS = increased life span.

[d] ITS = inhibition of tumor size.

[e] This group (placebo control) was used to calculate ITS and ILS for treated groups.

AZO = aziridinylbenzoquinone; CPA = cyclophosphamide each group consisted of 6 male mice, except for experiments CM 33 and CM 36, in which there were 8 females per group. In experiments on combined therapies, all of 46 control mice given only ip injections of NaCl solution or fed placebo beadlets died of progressively growing ASB XIII cancers.

Trials were made to test whether efficacy of PCNU versus ASB XIII might be enhanced by addition of a retinoid to food. As described elsewhere (21), mice in our laboratory were found to eat an average of 4 grams of unpelleted food (Purina Mouse Chow) per day. For experiments described in the present paper, a retinoid was mixed into this food to provide 10 mg/kg for a 20-gram mouse per day from Day 2 through Day 28 after transplant. Retinoids tested were Ro 1-5488 (all-trans retinoic acid) and its ester Ro 10-9359 (trimethylmethoxyphenyl analog ethyl ester). Ro 10-9359 was received as a powder, Ro 1-5488 in gelatin beadlets. Placebo beadlets contained corn oil instead of a retinoid. Retinoids and placebo beadlets were supplied by Hoffmann-LaRoche, Inc., Nutley, NJ.

Findings in experiment CM 31 (6 male mice per group) are shown in Table 3. PCNU was given Days 7, 14, 21 and 28. There was no ITS, no increase in lifespan and no CRs after either retinoid alone; there were no CRs in controls. There was ITS but no CRs after PCNU without retinoids. There were 3 CRs after treatment with the 15 mg/kg regimen of PCNU plus Ro 10-9359 and 3 CRs after the 8 mg/kg regimen of PCNU plus Ro 10-9359, and a single CR after the 15 mg/kg regimen plus Ro 1-5488. This experiment was briefly reported (20). As reported, ILS for mice without CRs on 15 mg/kg regimens were 56% for PCNU plus Ro 1-5488 and 33% for PCNU plus Ro 10-9359. Those calculations are based on median survival. Based on average survival, ILS is 41% in both these groups.

Animals in the control group died between 35 and 89 days after transplant. The 7 CRs in this experiment lived until they were sacrificed at 127 days. In the group on 15 mg/kg PCNU without retinoids, all 6 mice died between 41 and 44 days after transplant. They were in one cage and their deaths were attributed to contemporaneous disease. In an experiment with 10 mice bearing ASB XIII, treatment with 15 mg/kg PCNU 1 × q week × 7 gave one CR; the 9 others survived 56–90 days (Table 2). Table 2 also shows that no CRs of ASB XIII occurred in 10 mice that survived 52–82 days after PCNU 8 mg/kg 1 × q week × 7.

In experiment CM 37 (Table 3) groups of 6 mice were treated with 8 mg/kg PCNU on the same regimen as in CM 31 (1 × q week × 4), with and without retinoids. In the group treated with PCNU without retinoids, there was 41% ITS, 50% ILS and one CR. In the group on PCNU plus Ro 1-5488, there was 35% ITS and 21% ILS. In the group on PCNU plus Ro 10-9359, there was 53% ITS but lifespan was about the same as that of controls. In CM 37, there were no CRs in groups treated with retinoids, with or without PCNU.

As also shown in Table 3, experiment CM 37 included trials in groups of 6 mice treated with CPA 50 mg/kg im on Days 7, 14, 21 and 28, with and without retinoids (10 mg/kg) in food. In the group treated only with this regimen of CPA, ITS was 29% but average survival was the same as in saline/placebo controls. The group on CPA plus Ro 1-5488 had 29% ITS and 15% ILS. In the group on CPA plus Ro 10-9359, there was 65% ITS, but 3 animals in that group died before controls. A CR in that group cannot be attributed to Ro 10-9359, since a single CR occurred in experiment CM 36 after treatment with CPA 50 mg/kg × 3.

In trials by others, mice bearing transplants of colon adenocarcinoma no. 51 responded to PCNU or to 6-thioguamine (6-TG) as single agents and cures were obtained by combined therapy with these drugs (23). Using groups of 6 male mice with ASB XIII, we ran trials of 6-TG subcutaneously on days 7, 14 and 21, with and without PCNU ip 4, 8 or 15 mg/kg on the same days. CRs in the groups on those regimens of PCNU without 6-TG were 0, 2 and 1, respectively. In groups on those regimens of PCNU plus 4 mg/kg 6-TG, CRs were 1, 0, 2, respectively. With 6-TG alone, there was 44% ILS. Trials of 6-TG at 8 or 12 mg/kg were toxic.

In CM 33, groups of 8 female mice were treated on Days 7, 14 and 21 with CPA 100 mg/kg or aziridinylbenzoquinone (AZQ) 9 mg/kg, with and without PCNU 15 mg/kg, on the same days. With PCNU as a single agent there was one CR. With CPA as a single agent there were 7 CRs that lived until they were sacrificed, at 120 days. In the group treated with CPA and PCNU there were 4 CRs, but all mice in this group died between 66 and 84 days after transplant. This combined therapy cured the tumors, but toxicity may have killed their hosts. In the group treated with AZQ as a single agent there was 25% ITS at Day 28 and 33% ILS, but no CRs. In the group treated with PCNU plus AZQ, 7 animals died without tumors between 13 and 27 days after transplant. The one survivor in that group died without tumors at 104 days. Presumably, combined therapy at these doses cured the tumors but killed their hosts.

In CM 36, there were 8 female mice in each group. There was one CR after CPA as a single agent of 50 mg/kg im on Days 7, 14 and 21. There were 5 CRs after that regimen of CPA plus PCNU 7.5 mg/kg ip on these days. In another group in the same experiment, after treatment with the same regimen of CPA but with the addition of PCNU 15 mg/kg ip Days 7, 14 and 21, ITS was 80%, but ILS only 25% and there were no CRs.

Another squamous cell carcinoma (LC 12) was available in our laboratory for serial transplant to thigh muscles of BALB/c mice from our breeding colony. It was induced from fetal mouse lung cells by a polycyclic hydrocarbon (methylcholanthrene) and has been described and illustrated (13). Chemotherapy trials were run with groups of 6 male mice bearing transplants of LC 12. A first experiment with PCNU at 15 or 8 mg/kg 1 × q wk × 7 showed no CRs and little effect on tumor size or survival. In a second experiment, there were no CRs in mice treated only with PCNU or in controls, but there was one CR in mice on a diet to which Ro 10-9359 had been added and one CR in mice on this diet plus ip injections of 8 mg/kg PCNU 1 × q wk × 4. Tumor size at Day 28 in the 6 mice on the Ro 10-9359 diet without PCNU was 0, 0, 8, 8, 9, 11 mm. In a saline/placebo control group at Day 28, it was 12, 13, 13, 15, 15, 18 mm. In a saline control group, it was 12, 13, 13, 14, 15, 15 mm. The single CR in the group on the Ro 10-9359 diet without PCNU lived until Day 120, when he was sacrificed. The other mice in his group died with tumors at 73, 84, 94, 97 and 111 days. Survival in the two control groups ranged from 65 – 90 days. The diet containing Ro 10-9359 for this experiment was prepared to provide 10 mg/kg, as in the experiments with ASB XIII, and was given through Day 28.

Cryopreserved cells, identified as pulmonary carcinoma LC 12 and pulmonary carcinoma ASB XIV, are available from the Tumor Bank, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. ASB XIII is not available, as it did not "take" regularly in BALB/c mice from sources other than our breeding colony.

Discussion

In trials of nitrosoureas vs. transplants of a spontaneous anaplastic epidermoid carcinoma of the lung in mice (Lewis lung carcinoma), cures were achieved by treatment with PCNU (24). In clinical trials, however, PCNU was not effective for treatment of lung cancer (25). There were partial responses in only 2 of 22 adenocarcinomas, 2 of 11 large cell carcinomas, 2 of 15 small cell carcinomas and none of 13 squamous cell carcinomas (25). In these trials, PCNU was used as a single agent.

In experiments with mice detailed in the present article, PCNU as a single agent was effective for treatment of a large cell carcinoma (ASB XIV) but was seldom effective for treatment of a squamous cell carcinoma (ASB XIII). Response of ASB XIII was enhanced in some trials by combined therapies with PCNU and either Ro 10-9359, CPA or AZQ. PCNU produced no CRs for another squamous cell carcinoma (LC 12) but Ro 10-9359 caused marked growth inhibition. There was one CR of LC 12 after PCNU plus Ro 10-9359 and one CR after Ro 10-9359 alone.

Ro 10-9359 was found to inhibit induction of papillomas and carcinomas by a polycyclic hydrocarbon carcinogen on skins of mice (26). Clinical trials were made with advanced squamous cell carcinomas of the lungs treated by combined therapy with bleomycin and a nitrosourea (CCNU) with and without Ro 10-9359 in a preparation marketed as etretinate (27). Partial remissions (25 – 50% reduction in tumor size) were found in 3 of 25 patients treated with these drugs without Ro 10-9359 and in 5 of 21 treated with these drugs plus Ro 10-9359. This difference was not statistically significant, nor was survivorship in either of these groups. In these trials Ro 10-9359 was given orally 1 mg/kg daily for 6 weeks. In experiments showing inhibition of chemically induced papillomas and carcinomas of the skins of mice, Ro 10-9359 was given by stomach tube 30 mg/kg five days a week for 36 weeks (28).

In experiments reported elsewhere (29), responses of ASB XIII and ASB XIV were not notably different in males and females, and there was no notable difference in survivorship between the treated or control groups.

Relationships between vitamin A and retinoids have been summarized (29). In 2,592 patients, of whom 60% had cancers of the oral cavity or larynx and 40% had non-small-cell cancers of the lungs, treatments were found not to gain effectiveness from daily intake of high doses of vitamin A (retinyl palmitate) over a two-year period (30). Large-scale epidemiologic studies have found that long-term continued intake of high doses of vitamin A increases, rather than decreases the incidence of lung cancer (31). Biologic effects of retinoids has been reviewed (32, 33), and toxicity, including teratogenicity, has been summarized (33). Findings of abnormalities in fetuses preclude use of isotretinoin (13-cis retinoic acid) and etretinate (Ro 10-9359) during pregnancy.

Combined therapy with 13-cis retinoic acid and interferon-alpha has been found to be effective in clinical trials for treatment of squamous cell carcinomas of the skin (34) and cervix (35). For treatment of lung cancers with this combination, clinical trials arranged by the National Cancer Institute are in progress.

Conclusion

Chemotherapy trials were run with mice bearing transplants of carcinomas originally induced from fetal mouse lung cells by asbestos. In trials of nine drugs as single agents, complete remissions of a large cell carcinoma (ASB XIV) were obtained only with a nitrosourea (PCNU): 19 CRs in 40 mice. Treatment of a squamous cell carcinoma (ASB XIII) with PCNU was less effective: 6 CRs in 66 mice.

Response of ASB XIII was enhanced by combined therapy with PCNU and a retinoid (Ro 10-9359) in two of three trials. High doses of cyclophosphamide gave 7 CRs of ASB XIII in 8 mice. Combined therapy with low doses of cyclophosphamide and PCNU gave 5 CRs of ASB XIII in 8 mice. AZQ increased lifespan but gave no CRs of ASB XIII as a single agent. After toxic combined therapy with AZQ and PCNU, there were CRs in all of 8 mice. PCNU as a single agent gave no CRs of a squamous cell carcinoma (LC 12) originally induced from fetal mouse lung cells by a polycyclic hydrocarbon. Ro 10-9359 inhibited growth of LC 12.

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Interrelationship between Thyroid Nodularity and TSH Level

Isaac Sachmechi, M.D.[1], Marjan Vahedi, M.D.[2], Shireesha Nalamasu, M.D.[2], and Raj Vuppalanchi, M.D.[3]

Abstract

Background: The pathophysiological role of thyroid-stimulating hormone (TSH) in the development of goiter is controversial. The aim of this study was to examine the relationship between thyroid nodularity and serum TSH levels in clinically and biochemically euthyroid patients with non-endemic multinodular goiter.
Methods: We surveyed 44 of our endocrine clinic patients with multinodular goiter. Twenty-five patients with suppressed TSH levels or positive antithyroid antibodies were excluded. The remaining 19 patients were included (group 1). The 19 study subjects were compared with 19 age- and sex- matched controls without any thyroid disease or goiter (group 2). TSH levels in both groups were checked by review of their medical records.
Results: In group 1, TSH ranged from 0.68 – 3.68 IU/mL (normal: 0.4 – 6.0 IU/mL), with a mean of 1.45±0.29. In group 2, TSH ranged from 0.38 – 1.88 IU/mL, with a mean of 1.08±0.1. The differences of these values, analyzed by paired t test ($p=0.22$), were not statistically significant.
Conclusions: These data suggest that TSH levels in euthyroid patients with multinodular goiter are not significantly different from those in normal controls.
Key Words: Thyroid nodularity, thyroid-stimulating hormone, goiter.

Introduction

The term "nontoxic goiter" refers to diffuse or nodular thyroid gland enlargement that is not associated with hyperthyroidism or hypothyroidism. In the United States, nontoxic goiter affects more than 5% of the population (1). In the geographic regions where nontoxic goiter affects more than 10% of the population (e.g., areas with iodine deficiency or environmental goitrogens), the term "endemic goiter" is used (1).

The pathophysiological role of thyroid-stimulating hormone (TSH) in the development of goiter is controversial. Some studies report *in-vitro* stimulatory effects of TSH on thyroid cell growth (2). Other studies suggest that TSH is not a growth factor for human thyroid cells in culture (3, 4). The aim of this study was to examine whether or not there is a relationship between TSH level and nodularity in euthyroid, non-endemic multinodular goiter patients.

Patients and Methods

A retrospective survey of 44 consecutive patients with multinodular goiter (30 women and 14 men) attending our endocrine clinic was conducted ("multinodular goiter" was defined as the thyroid gland having two or more nodules). Thyroid nodularity by palpation was confirmed by ultrasonography. Twenty-five patients who had either decreased TSH or positive antithyroid antibodies were excluded from the study. The remaining 19 patients (12 women and 7 men) were included and their TSH levels were recorded from their medical records. These values were compared to TSH levels obtained from chart reviews of 19 age- and sex-matched control subjects without thyroid disease or goiter.

Results

The serum TSH concentration in the patient group with multinodular goiter ranged from 0.68 – 3.68 IU/mL (normal: 0.4 – 6.0 IU/mL), with a mean of 1.45±0.29. In the control group, the range of

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[1] Chief, Division of Endocrinology and [2] Resident, Department of Medicine, Mount Sinai Services, Queens Hospital Center, Jamaica, NY, and [3] Resident, Department of Medicine, Long Island College Hospital, Brooklyn, NY.

Address all correspondence to Isaac Sachmechi, M.D., Chief, Division of Endocrinology, Department of Medicine, Mount Sinai Services, Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432; e-mail: sachmeci@nychhc.org

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TSH was 0.38 – 1.88 IU/ml, with a mean of 1.08±0.1. These values were analyzed using a paired t test (p=0.22). The difference was not statistically significant (Table).

Discussion

Non-endemic goiter has been attributed to thyroid-stimulating immunoglobulin, hereditary defects in the biosynthesis of thyroid hormone, exposure to radiation, nutritional defects, excessive iodine intake from drugs or food, and environmental goitrogens (1).

We demonstrated that TSH levels in euthyroid patients with non-endemic multinodular goiter are not significantly different from those of controls. Our clinical observations suggest that the pathophysiological role of TSH in goitrogenesis may be less important than has been assumed so far. In fact, some of the *in-vitro* studies of human thyroid follicular cells in tissue culture indicate that TSH is not a growth factor and indeed may inhibit cellular proliferation (3, 4). In a study by Gharib et al. (5), the efficacy of levothyroxine therapy in reducing the size of colloid thyroid nodules was not apparent within six months, despite effective suppression of TSH, suggesting that TSH is not the cause of the nodular goiter. Weber et al. (6) found that mean 24-hour serum TSH levels and the nocturnal surge of TSH levels were not different in a group of 11 patients with multinodular goiter and 11 healthy controls. Furthermore, TSH levels decrease with age in humans, but the presence of goiter increases with age (7).

TABLE 1

The Comparison of TSH Levels between the Multinodular Goiter Patient Group and the Control Group.

TSH levels in the multinodular goiter patient group (IU/mL)	TSH levels in the control group (IU/mL)
1.19	1.77
0.93	1.887
1.39	0.54
0.68	0.57
2.46	0.99
0.7	1.11
0.99	0.621
1.43	1.007
3.25	1.16
0.99	1.41
3.68	1.64
0.85	1.403
0.89	1.3
0.73	0.79
1.27	1.38
1.042	0.66
1.19	0.38
3.06	0.795
0.83	1.08
Range: 0.68-3.68	Range: 0.38-1.88
Mean: 1.45±0.29	Mean: 1.08±0.1

Wahner and colleagues (8) found that goiter in Cauca Valley, a forest in Colombia, was not dependent on increased TSH levels. However, an increased sensitivity to normal levels of TSH induced by the action of a goitrogen may exist.

Bray (9) proposed the hypothesis that the explanation for normal TSH levels in the presence of goiter is that the iodine-deficient gland is more sensitive to the goitrogenic properties of TSH (10, 11). Our observations also do not support the assumption that increased TSH levels correlate with goiter. However, some studies suggest a correlation between increased TSH levels and multinodular goiter. Though goiter in Cauca Valley was not dependent on increased TSH, the microscopic study of the excised thyroid of a 14-year-old girl from there, who was killed in an accident, suggested TSH stimulation of the gland (8). Young et al. found high TSH levels in 42% of 51 patients with idiopathic euthyroid goiter (12). In another study, in the iodide-deficient desert of New Valley, Egypt, TSH levels were higher in goitrous young men compared to nongoitrous young men who drank water with higher iodine concentration (13), showing that TSH is a contributing factor in endemic goiter (14).

Circulating TSH might be the main factor responsible for goiter in patients with Hashimoto's thyroiditis and clinical hypothyroidism (15). Bucker-Davis et al. (16) reported the presence of goiter in 80% of 25 patients with TSH-secreting tumors of the pituitary. Thyroid nodules were detected in 64% of the cases, either clinically or by ultrasonography.

Conclusion

Our study indicates that TSH levels in euthyroid patients with non-endemic multinodular goiter are not significantly different from those in normal controls. Since the published studies on the role of TSH and the cause of nodularity in the thyroid gland are inconclusive, more studies are needed to confirm these findings, and to investigate and detect other factors that may be involved in the causation of multinodular goiter.

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Barriers to Colorectal Cancer Screening:

Inadequate Knowledge by Physicians

Melissa Gennarelli, M.D.[1], Lina Jandorf, M.A.[1], Caroline Cromwell, M.D.[1],
Heiddis Valdimarsdottir, Ph.D.[1], William Redd, Ph.D.[1], and Steven Itzkowitz, M.D.[2]

Abstract

Background: The rate of colorectal cancer (CRC) screening remains relatively low. One potential barrier to higher rates is the lack of physician knowledge regarding CRC screening. The purpose of this study was to assess physicians' knowledge of (a) American Cancer Society (ACS) CRC screening guidelines for average-risk and high-risk patients, and (b) general colorectal cancer facts which support these guidelines.

Methods: We administered a questionnaire to internal medicine residents, internal medicine attendings and medical students who provide care to patients in a low-income, predominantly minority community, to compare their levels of knowledge regarding CRC screening. Mean knowledge scores were calculated based on the number of correct responses.

Results: Knowledge of ACS guidelines for average-risk patients was low, although it did increase directly with level of training: medical students obtained a mean score of 32%, residents 49%, and attendings 56% ($p<0.001$). Knowledge scores for high-risk patients were even lower, with fewer than half of the respondents offering correct answers. Mean knowledge scores of general CRC screening facts increased with level of training: medical students scored 31%, residents 38% and attendings 42% ($p<0.001$).

Clinical Implications: Knowledge of CRC screening guidelines for both average- and high-risk patients was suboptimal among the medical students, residents and attendings studied. Lack of knowledge about CRC is one barrier to screening that may contribute to underutilization of screening for minority populations. Further educational efforts should be targeted to these health care professionals.

Key Words: Colorectal cancer, cancer screening, ethnic minorities, colonoscopy, sigmoidoscopy, fecal occult blood test, ACS guidelines.

Introduction

COLORECTAL CANCER (CRC) is the second most common cause of cancer-related deaths in the United States. Screening asymptomatic individuals for lesions predisposing to CRC reduces morbidity and mortality, and is cost effective. In recent years, studies have investigated physician practices and found that not all patients are being screened for CRC at intervals recommended by national organizations (1–5). Medical associations are aware of the appropriate clinical guidelines for CRC screening and surveillance for average- and high-risk individuals; nevertheless, screening rates remain unacceptably low. Studies show that the single most important predictor of patient compliance with CRC screening tests is physician recommendation (6, 7). Primary care physicians (PCP) in particular are in a unique position to provide CRC screening. They also play a critical role in recommending and encouraging patient acceptance of screening tests.

Rates of CRC screening in the U.S. are relatively low despite compelling evidence that CRC screening saves lives. According to CDC data from the 1999 Behavioral Risk Factor Surveillance System (BRFSS), only 40.3% of respondents over the age of 50 reported ever having had a fecal occult blood test (FOBT) and only 43.8% reported ever having had a sigmoidoscopy (8). In 1999 the state of New York reported via the BRFSS that only 34.6% of whites, 28.6% of African Americans, and 21.3% of Hispanics had ever had a sigmoidoscopy or colonoscopy (9). These rates are unacceptably low, especially compared with screening for breast, cervical and prostate cancer. Rates of FOBT and sigmoidoscopy are even lower when evaluated for the American Cancer Society (ACS) recommended time intervals. It is particularly disconcerting that CRC screening rates are lower among African Americans despite the higher incidence and mortality of CRC in this group. For screening to be effective in reducing morbidity and mortality from CRC, it should be performed on a regular basis. However, the prevalence of repeat screening in the U.S. has been reported to be low for both flexible sigmoidoscopy and FOBT (10, 11).

From the [1]Derald H. Ruttenberg Cancer Center, and [2]Department of Medicine, Mount Sinai School of Medicine, One East 100th Street, New York, NY.

Address all correspondence to: Lina Jandorf, M.A., Box 1130, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: lina.jandorf@mssm.edu

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The reasons for the low rates of CRC screening include organizational, patient-related, and physician-related factors. In the present study, we examine one of the physician-related factors. Although some studies have examined physicians' knowledge base as a potential barrier to CRC screening (12–17), none have specifically surveyed medical students, residents, and attendings since the revision of the guidelines in 1997. A recent article assessing resident knowledge of colorectal cancer identified only one area of deficiency, lack of knowledge regarding proper management of a positive FOBT (13). Another article reported deficient knowledge among internal medicine residents regarding screening recommendations for high-risk groups (18). The inclusion of medical students, residents, and attendings in our study was done in an effort to assess knowledge across all stages of medical education in order to better define the population(s) and specific areas in need of intervention.

Many studies examining physician behavior with regard to CRC screening have used the terms "practice" and "knowledge" interchangeably. Such studies have found that physician practices are not consistent with the recommended guidelines, and some studies presume that this is due to inadequate physician knowledge without directly assessing this knowledge (18, 19). Physician practices may be altered by a host of barriers, only one of which is knowledge. Sharma et al. (20) assessed primary care physician (PCP) knowledge and practice of CRC screening, through the use of six hypothetical patient scenarios. The study detected some important discrepancies between self-reported PCP practices and national guidelines. The authors suggested that these inconsistencies in physician practices were a direct result of imperfect understanding and deficient knowledge on the part of the PCP (19). A second study by the same group assessed internal medicine residents' practices with regard to CRC screening. The questions in both of these studies actually assessed physician's personal practice or opinions with regard to CRC screening, but neither study directly assessed physician's knowledge and awareness of the recommended guidelines. We therefore developed a survey to directly evaluate the physician's knowledge base with regard to CRC.

Materials and Methods

Development of Physician Survey Instrument

Institutional Review Board (IRB) approval was obtained to administer the questionnaire to all eligible participants. (For participant criteria, see **Study Design**, below.) Questions were designed to elicit information regarding physicians' knowledge of: (A) CRC screening guidelines for average-risk patients; (B) CRC screening guidelines for high-risk patients; and (C) general CRC facts. The guideline questions (sections A and B) assessed physicians' knowledge of nationally accepted guidelines for CRC screening recommendations. Questions were developed to be consistent with both the American Cancer Society (ACS) and the 1997 multidisciplinary panel recommendations (21). Physicians were asked specifically to answer questions based on ACS recommendations, not on their current practices. Physicians were asked what the ACS recommendations are for both the starting age and frequency for each of the following CRC screening options: FOBT, flexible sigmoidoscopy (FS), and colonoscopy. In section B, five case vignettes were created to assess physician's knowledge of screening and surveillance guidelines for high-risk patients. High-risk patients were defined as individuals with a family history of cancer, adenomatous polyps, familial adenomatous polyposis (FAP), hereditary nonpolyposis colon cancer (HNPCC), and/or a personal history of adenomatous polyps. Section C consisted of multiple-choice questions, derived from the current literature, assessing factual knowledge that is used to support the recommended guidelines. Three national experts reviewed the questions independently for fact and content validity.

Study Design

This study was conducted at four major medical centers serving the low-income, medically underserved community of East Harlem in New York City. Participation was limited to third or fourth year medical students (n=53), internal medicine residents (n=92), or internal medicine attendings (n=23). To ensure construct validity, the survey was first administered to 7 gastroenterology fellows and 14 oncology nurses who served as positive and negative controls, respectively (Table 1). After the questionnaire was administered, we compared the knowledge scores of the three groups (medical students, residents, attendings), using analysis of variance (ANOVA). All statistical analyses were performed using SPSS, version 10.0.

Data Collection and Procedures

Participants were unaware of the subject matter addressed in the survey prior to its administration, to prevent any preparation ahead of time. The survey was voluntary and anonymous. Within each section of the questionnaire, cumulative knowledge scores based on the number of correct answers were calculated for each participant.

TABLE 1
Knowledge of CRC Screening Guidelines and Facts Among Study Participants and Controls

	Knowledge of ACS guidelines for average-risk patients		**Knowledge of ACS guidelines for high-risk patients**		**Knowledge of general CRC screening facts**	
	No. people responding	**Mean Score**	**No. people responding**	**Mean Score**	**No. people responding**	**Mean Score**
Oncology nurses (n=14)	9	42%	10	37%	13	20%
Medical students, Residents, attendings (n=168)	158	46%[a]	164	53%[a,b]	168	37%[a,b]
Gastroenterology fellows (n=7)	7	81%	7	83%	7	69%

[a] p<0.05 for target group (medical students, residents and attendings) knowledge compared to gastroenterology fellows
[b] p<0.05 for target group knowledge compared to oncology nurses
ACS = American Cancer Society, CRC = colorectal cancer

Results

A total of 400 surveys were distributed, with a response rate of 48%. Of the 195 respondents, 27 did not meet study criteria (18 specialists, 4 nurse practitioners, and 5 physician assistants) and were excluded from the analysis. The demographics of the three groups are shown in Table 2. Because the survey was anonymous, we do not know the demographics of the nonresponders.

Comparison of Knowledge Scores by Training

Knowledge scores on all sections were progressively higher as level of training increased (Table 3). Indeed, within each group, scores also increased with level of training (e.g., years of medical school and from postgraduate year one (PGY-1) to PGY-2 to PGY-3, such that PGY-3 and PGY-4 residents had knowledge levels equivalent to those of attendings (data not shown).

Knowledge of Average-Risk Patient Guidelines (Section A)

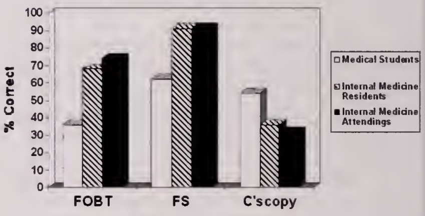

Fig. 1. Participants were asked at what age does the American Cancer Society (ACS) recommend to begin screening for patients who have no family history of colorectal cancer (CRC). C'scopy = colonoscopy, FOBT = fecal occult blood test, FS = flexible sigmoidoscopy.

Fig. 1 depicts the percentage of correct responses regarding the recommended starting age for the three major colon cancer screening tests. The correct response (age 50) was identified by the following percentage of internal medicine residents: FOBT (68%), FS (91%), and colonoscopy (36%). The responses of residents more closely approached those of the attendings than those of the medical students.

With respect to knowing the frequency for performing screening tests according to ACS guidelines, 84% of residents correctly indicated FOBT should be done annually and 71% knew that FS is recommended for every 5 years, but only 24% were aware that colonoscopy is recommended for every 10 years (Fig. 2). For all three tests, the rate of cor-

TABLE 2
Demographics

	Age (Mean Years / SD)	Gender (% Male)	Ethnicity (% White)
Medical students (n=53)	25.8 / 1.7	36%	56%
Internal medicine residents (n=92)	29.6 / 4.0	65%	59%
Internal medicine attendings (n=23)	39.4 / 10.2	61%	61%

TABLE 3

Knowledge of CRC Screening Guidelines and Facts Among Study Participants

	Knowledge of ACS guidelines for average-risk patients		Knowledge of ACS guidelines for high-risk patients		Knowledge of general CRC screening facts	
	No. people responding	**Mean Score**	**No. people responding**	**Mean Score**	**No. people responding**	**Mean Score**
Medical students (n=53)	52	37%[a,b]	53	53%	53	31%[a,b]
Internal medicine residents (n=92)	83	49%	90	52%	92	38%
Internal medicine attendings (n=23)	23	56%	23	54%	23	42%

[a] p<0.05 for medical students compared to residents
[b] p<0.01 for medical students compared to attendings
ACS = American Cancer Society, CRC = colorectal cancer

rect responses by residents was somewhere between that of medical students and internists.

Knowledge of High-Risk Patient Guidelines (Section B)

Physicians were provided with five vignettes to test knowledge of recommended guidelines for screening high-risk patients (Table 4). The first vignette described an asymptomatic patient with a single first-degree relative diagnosed with CRC at an age less than 55. All participants scored high on this vignette, knowing the correct age to begin screening (40 years old), with an overall correct response rate of 60%. The second vignette described an asymptomatic patient with a single affected first-degree relative diagnosed with an adenomatous polyp of the colon at age less than 60. Only 28% of residents correctly chose age 40 as the recommended screening age. The third vignette tested knowledge of what age to begin screening of an asymptomatic patient with a known family history of FAP. Only 36% of residents knew to begin screening at age 12, and the vast majority (88%) chose colonoscopy rather than the recommended FS (11%) as the screening test.

The fourth vignette was of an asymptomatic patient with a known family history of HNPCC. Of the residents, 43% would correctly begin screening for CRC while the patient was in his twenties. Medical students and attendings had a slightly lower correct response rate on this case. The fifth vignette was of a 65-year-old man who had removal of a 1.5 cm polyp. Forty-eight percent (48%) of residents knew that surveillance colonoscopy should be performed 3 years after the procedure, compared with 27% of the medical students and 65% of the attendings.

Knowledge of General Cancer Facts (Section C)

Results of selected questions (for the residents) that test knowledge of the screening tests which form the basis of the ACS guidelines are presented in Figs. 3 and 4. Fact one: FOBT performed annually for asymptomatic patients has been shown to decrease mortality by 30–35% (22). Only 18% of res-

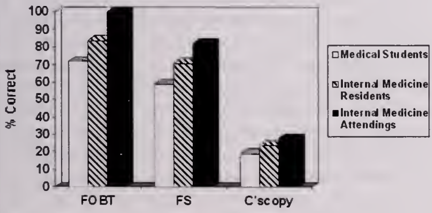

Fig. 2. Participants were asked at what frequency does the ACS recommend each of these screening tests for patients who are due for CRC screening and who have no family history of CRC.
For explanation of abbreviations, see Fig.1.

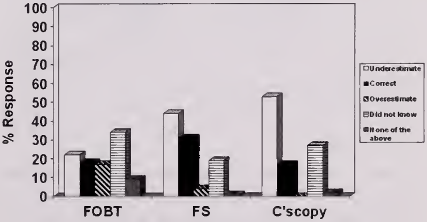

Fig. 3. Internal medicine residents' responses to efficacy rates of different procedures.
For explanation of abbreviations, see Fig.1.

TABLE 4

Vignettes Evaluating Physician Knowledge of Screening and Surveillance Guidelines for High-Risk Patients. Physicians Were Asked to Answer Questions on the Following Cases with Regard to the American Cancer Society (ACS) Screening Recommendations.

Vignette	Question	Medical Students No. correct respondents / No. people responding	Internal Medicine Residents No. correct respondents / No. people responding	Internal Medicine Attendings No. correct respondents / No. people responding
An asymptomatic patient with a single affected first degree relative diagnosed with CRC at age less than 55.	At what age should this patient begin screening for CRC? Answer: 40	29/52 (56%)	56/89 (63%)	14/23 (61%)
An asymptomatic patient with a single affected first degree relative diagnosed with an adenomatous polyp of the colon at age less than 60.	At what age should this patient begin screening for CRC? Answer: 40	26/51 (51%)	25/90 (28%)	9/23 (39%)
An asymptomatic patient has a family history of familial adenomatous polyposis (FAP).	At what age should this patient begin screening for CRC? Answer: 12	25/51 (49%)	32/88 (36%)	7/22 (32%)
An asymptomatic patient has a family history of hereditary nonpolyposis colon cancer (HNPCC).	At what age should this patient begin screening for CRC? Answer: 25	21/50 (42%)	38/89 (43%)	7/23 (30%)
A 65-year-old man has just had a colonoscopy which revealed a single 1.5 cm adenomatous polyp.	When should you recommend that this patient have a repeat test? Answer: 3 years	12/44 (27%)	40/84 (48%)	15/23 (65%)

CRC = colorectal cancer

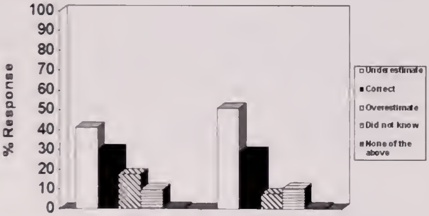

Fig. 4. Internal medicine residents' responses to risks of different procedures.
For explanation of abbreviations, see Fig.1.

idents knew the correct answer, 22% underestimated, 17% overestimated, and the remainder either did not know the efficacy or chose "none of the above." Fact two: Sigmoidoscopy has been shown to decrease mortality from distal CRC by 65–70% (23, 24). Only 31% of residents correctly chose this response, while 44% underestimated the efficacy of sigmoidoscopy, 4% overestimated, and the remainder either did not know or chose "none of the above." Fact three: Colonoscopy with polypectomy has been shown to decrease the expected incidence of CRC by over 85% (25). Only 17% of the residents correctly chose this answer, 53% underestimated the efficacy of colonoscopy, 27% did not know, and 2% chose "none of the above." Two questions assessed the risk of FS and colonoscopy. Best estimates of the risk of colonic perforation from these tests are 1/10,000 from FS and 1/1,000 from colonoscopy (21). Thirty percent (30%) and 29% of residents correctly estimated the risk of FS and of colonoscopy, respectively. As shown in Table 2, resident overall factual knowledge with regard to CRC was somewhere between that of medical students and attendings.

Discussion

The present study showed that knowledge of CRC screening guidelines among medical professionals is low for both average-risk and high-risk patients. Colorectal cancer is a major preventable public health problem in the United States. Data from the 1999 BRFSS demonstrate low CRC screening rates in the general population for FOBT, FS, and colonoscopy (26). CRC screening rates appear to be even lower nationally among minority groups, including African-Americans and Hispanic-Americans, as compared to Caucasians (26). Although important efforts are underway to enhance public awareness of CRC screening, attention must also be given to enhancing physician knowledge and awareness. Since internists are often on the frontlines of CRC screening, we chose to investigate the knowledge of primary care physicians at all levels of training.

Average-Risk Patients (Section A)

Section A assessed physicians' knowledge of available screening options as recommended by the ACS. The ACS recommendations were used as the standard for comparison, since prior studies have indicated that the majority of physicians follow or agree with these guidelines as compared to those of other national organizations (27–29). In addition, the ACS guidelines are consistent with those of the 1997 multidisciplinary panel (21). At the time of this survey, the ACS recommended as suitable screening options for average-risk patients: (a) FOBT annually and FS every 5 years; (b) colonoscopy every 10 years; and (c) double contrast barium enema every 5–10 years.

As reported in the results section, physicians at all levels of training demonstrate low levels of knowledge of the screening guidelines for average-risk patients. Although knowledge scores increased incrementally according to level of training, they did not exceed 56% for any group. This lack of knowledge is likely to have a direct impact on physicians' screening practices. If physicians are unaware of the acceptable and alternative options for CRC screening, they may not select the appropriate, individualized test for the patient. Physicians should be knowledgeable about all available screening methods for CRC so that patients can be informed about their options and make educated medical decisions. In one study assessing internal medicine residents' practices, 71% of residents would begin screening for CRC at age 50 (20). In our study, the percentage of correct responses to this issue among the residents was even lower; approximately one third of residents did not know that 50 is the recommended age to begin FOBT testing. While the majority of residents knew the correct age to begin recommending FS, almost half of all residents did not know that colonoscopy is recommended as a CRC screening option for average-risk patients.

Although most residents knew the recommended frequency for FOBT (80%), approximately one third of residents did not know the frequency for FS and less than one third correctly identified the frequency for colonoscopy. Similar rates were obtained for medical students and attendings, with resident correct response rates being intermediate. Although it is true that physicians may be following the recommendations of other national organizations for CRC screening, we have chosen to assess knowledge of the most widely accepted guidelines. Furthermore, physicians should also be aware of recommendations put forth by other nationally recognized organizations in order to make informed decisions about which one they will follow in practice.

Knowledge of High-Risk Patient Guidelines (Section B)

We also aimed to assess physicians' knowledge of ACS guidelines for high-risk patients, since primary care providers are often the first to encounter and identify patients with a family history of CRC or other risk factors for CRC and subsequently refer them to a specialist.

Family history of CRC. Persons who are at a higher risk of developing CRC should be screened more aggressively. The higher an individual's risk of disease, the greater the potential benefit from screening for that person and the lower the cost of screening per cancer detected (21). Individuals with a family history of CRC are defined as those who have one or more first-degree relatives with CRC, excluding people with FAP and HNPCC. First-degree relatives of persons with CRC have consistently been found to have a 2–3-fold increased risk of CRC compared to control populations (30), and there is good evidence that cancers arise at an earlier age in these people than in average-risk persons. The risk of developing CRC for a 40-year-old person with a family history of CRC is comparable to that of an average-risk 50-year-old person (21, 30). A 5–10% reduction in mortality is predicted if individuals with a positive family history begin screening at age 40 rather than 50. For these reasons, it is recommended that CRC screening begin at age 40 or at ten years before the youngest case in patients with a first-degree relative who had CRC before the age of 55 years. Other groups have recommended guidelines for screening those with familial risk, but they also support the age criteria recommended by the ACS (9, 21, 31). In our study, more than one third of medical students, residents and attendings did not correctly identify the age at which screening should begin for patients who have a first-degree relative with CRC. This is somewhat worse than the 21% incorrect response rate among internal medicine residents reported by others (18).

There is also evidence that patients who have first-degree relatives with adenomatous polyps are at increased risk for CRC when the polyp is diagnosed before the age of 60 (21, 32, 33). These patients should also begin screening at age 40 or ten years younger than the index case. However, about two thirds of residents and attendings, and half of medical students did not know this. It is possible that physicians do not routinely ask patients about these risk factors because they are unaware that the information may lead to a change in medical management.

Genetic syndromes. Internal medicine physicians should also be aware of the screening recommendations for high-risk patients with a family history of genetic syndromes. The identification of a first-degree relative with FAP and/or HNPCC has direct implications for the patient's risk of developing CRC and for the physician's management of the patient and the patient's family members. According to recommended guidelines, FAP gene carriers and indeterminate cases should be offered FS every year beginning at puberty, or around age 12, to see if they manifest the phenotype. Although participants surveyed in our study thought that it is recommended to begin screening before the age of 50 for a patient with a family history of FAP, only one third of residents and attendings, and half of medical students knew the correct age to begin screening for FAP. Most participants chose an age over 25 (9, 21, 34).

HNPCC is also inherited in an autosomal dominant fashion and is characterized by an 80% risk of CRC. Risk of CRC increases by age 21 and is very high by age 40. Patients with a family history of CRC in multiple close relatives and across generations should receive genetic counseling and/or testing for HNPCC between the ages of 20 and 30. This age criterion is accepted by most national organizations, including ACS and the 1997 Multidisciplinary Task Force. Yet fewer than 45% of medical students, residents and attendings knew the correct age to begin screening for patients with a family history of HNPCC. Internal medicine attendings in our study had correct response rates similar to those of physicians in a study by Schroy et al. (12). It is unclear whether this lack of knowledge regarding high-risk patients reflects physician unfamiliarity with the actual diseases or with the recommendations for CRC screening.

Surveillance for patients with history of adenomatous polyps. One vignette was used to assess physician knowledge of optimal surveillance intervals, as recommended by the ACS, for patients with a history of adenomatous polyps. The National Polyp Study directly addressed the question of optimal surveillance intervals (35). The data from this study supports the ACS recommendation that follow-up surveillance colonoscopy need not be performed until 3 years after the removal of adenomas at the initial examination. Most physicians in our study knew that the surveillance test of choice for a patient with personal history of polyps > 1 cm is colonoscopy, but were not sure about the recommended frequency of future surveillance. Attendings were more familiar with this recommendation than were residents or medical students.

General Knowledge of CRC Facts (Section C)

This is the first study to date to assess actual physician knowledge of facts such as test efficacy and risk. Overall, physicians were unaware of screening test efficacy. Less than one third of residents chose the correct response when asked about the ability of each of these screening tests to decrease mortality from and incidence of CRC based on the current literature. In a study by Montano et al., physician belief in the efficacy of sigmoidoscopy positively correlated with rates of providing sigmoidoscopy (35). Similarly, perceived ineffectiveness of FOBT has been identified as a reason for physician not complying with the test (17). Low level of knowledge of actual test efficacy can be expected to affect perceived efficacy on the part of the physician and may partially account for the low usage of both FS and colonoscopy as screening procedures for average-risk patients. Interestingly, in our study, a larger percentage of physicians underestimated the efficacy of FS and colonoscopy than that of FOBT. This is consistent with the lower rates of screening endoscopy than FOBT which exist in this community.

Prior studies (36) have indicated that physicians' perception of the risks of sigmoidoscopy are also a barrier to its implementation. Surprisingly, residents in our study underestimated the actual risk of flexible sigmoidoscopy and colonoscopy. Perhaps even the underestimated risk rates are unacceptable to this group of physicians. Approximately two thirds of residents did not know the risk of perforation associated with FS and colonoscopy, as estimated in the current literature. An inadequate knowledge base in these crucial areas will lead to an incorrect estimation of risk-benefit ratio, which is necessary for selecting any screening or diagnostic test for a patient.

Implications

Overall, the knowledge level of CRC screening guidelines and medical facts is low among medical students, residents and attendings serving the medically underserved minority community of East Harlem. Scores assessing knowledge of guidelines for high-risk patients were similar, yet low, across all levels of training. This suggests a need for educational interventions with regard to CRC, beginning early in medical education. Increasing physician knowledge of current guidelines and clinical trial results will provide practicing physicians and physicians in training with the appropriate foundation for decision making and patient care with regard to CRC prevention and detection. Thus, as a next step, an intervention geared toward increasing physician knowledge of CRC guidelines should be explored.

There were several limitations to our study. First, although our response rate is similar to that of other physician-based surveys, we do not have data regarding the nonresponders (13). This may serve as a limitation to the external validity of our study. Second, although physicians were specifically asked about their knowledge of the ACS guidelines, they may have answered according to personal practices or to other guidelines that would falsely lower the obtained knowledge results. Lastly, we can report on level of physician knowledge, but cannot predict how this knowledge actually influences practice without some measure of physician compliance. Further studies could investigate whether knowledge is a significant predictor of practice.

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Corporal Punishment of Children in England and the United States:

Current Issues

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S., F.R.C.P.G.

Abstract

Proverbs has eight statements about beating children, but that book does not contain the often cited proverbial "spare the rod and spoil the child." This form of discipline, which is thousands of years old, has only recently been abandoned and forbidden in many states in the US, and in much of Europe. It is still legal in Britain and some US states, and remains a controversial issue.

Key Words: Child-beating, Europe, US, Canada.

CHILD-BEATING remains a contoversial medical and bioethical problem. The commonly cited maxim, "Spare the rod and spoil the child," is not a biblical commandment. Admittedly, the Book of Proverbs (1) has similar sentences: (10:13) A rod is ready for the back of the senseless; (13:1) A wise son...it is through the discipline of his father; (13:24) He who spares the rod hates his son, But he who loves him disciplines him early; (19:18) Discipline your son while there is still hope; (22:15) If folly settles in the heart of a lad, The rod of discipline will remove it; (23:13) Do not withhold discipline from a child; If you beat him with a rod he will not die, Beat him with a rod and you will save him from the grave; (26.3) A rod for the back of dullards; (29:15) Rod and reproof produce wisdom, But a lad out of control is a disgrace to his mother.

Proverbs is an anthology of contemporary Near Eastern wisdom literature compiled around the 5th century BCE. For example, in the time of Sennacherib, in the late 7th century BCE, an Assyrian sage, Ahiqar (who is mentioned in *Tobit*), wrote, "The son who is trained and taught and on [whose] feet the fetter is put [shall prosper]. Withhold not thy son from the rod, else thou wilt not be able to save [him from wickedness]. If I smite thee, my son, thou wilt not die, but if I leave thee to thine own heart [thou wilt not live]" (2).

In fourth century BCE Greece, Menander claimed that "he who is not flogged is not educated" (3). Even earlier, about 2000 BCE, Sumerian schoolchildren were criticized for pushing, shouting, quarreling and cursing. Conversely, these pupils complained of being caned merely for being late to arrive, early to leave, untidy, or for slouching, talking or standing without permission, not speaking Sumerian and having untidy handwriting (4). One rare exponent of moderation was the first century Alexandrian Pseudo-Phocylides: "Do not apply your hand violently to tender children.... Be not harsh with your children, but be gentle" (5).

Beating children was lawful. The Talmudic sages said that a father may beat his son and a teacher his pupil, but only with a shoe thong (6). "If being excessively angry, a father killed his son while punishing him, he is not (as in Roman law) immune from the consequences of his action: it is murder" (1). Today, it is manslaughter or the equivalent in most legal systems.

Corporal punishment has been a practice of both secular and religious education (7) in many societies in all centuries until recently. There is extensive literature on its use in British schools (8).

Victorian Britain relished beating children into obedience and duty, and felt that they were divinely commanded not to "spare the rod and spoil the child." As recently as 1904, an admiral cited King

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From the Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Dr. J.H. Baron, Division of Gastroenterology, Box 1069, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029-6574.

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Solomon, the legendary author of *Proverbs*, against George Bernard Shaw, who maintained that "the cane and the birch are essentially a fool's implements" (9). Shaw demolished the admiral's arguments.

In Britain, the law permitting the caning of children dates from 1860, when "to correct what is evil in a child," parents could "inflict moderate and reasonable corporal punishment." The cane was outlawed in state schools in the 1986 Education Act. Beating is legal in English homes and private schools, provided parents agree with the school's code of discipline. In Britain, 74% of 11,600 adults surveyed reported that, as children, they had been punched, kicked or choked by their parents, and 35% of children of a sample of typical two-parent families had received severe physical punishment (9). However, the European Court is currently trying to compel Britain to ban such beating as a violation of Article 3 of the European Convention for the Protection of Human Rights. Britain is also in violaton of Article 19 of the 1989 UN Convention of the Rights of the Child, which requires signatories "to protect the child from all forms of physical violence" (10).

In the US 27 states have already banned corporal punishment in schools, beginning with New Jersey, in 1867. Yet the US Supreme Court in 1977 rejected the notion that such punishment was cruel, thereby allowing hundreds of thousands of children to be beaten each year in the 23 states where it is still legal (11). Since Canadian law forbids caning, one hundred families of the Church of God recently fled Ontario for the US as refugees, seeking political asylum in Ohio and Indiana on grounds of religious persecution, claiming that they were not being allowed to follow the word of God "to use the rod of correction" (12). Their literal fundamentalism forbids them to strike their children, because the hand is to be used to caress, so that any discipline would require the biblical rod. And the Canadian Supreme Court in January 2004 allowed parents to spank their 2 – 12 year-old children with only limited force (13). However, the English courts recently rejected a claim by teachers and parents of children in an independent school that their religious beliefs in corporal punishment for religious reasons was an article of religious faith for purposes of freedom of conscience in the European Convention of Human Rights (14).

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Correlation between Housestaff Performance on the United States Medical Licensing Examination and Standardized Patient Encounters

William D. Rifkin, M.D.[1], and Arthur Rifkin, M.D.[2]

Abstract

Background: There is interest in the use of "standardized patients" to assist in evaluating medical trainees' clinical skills, which may be difficult to evaluate with written exams alone. Previous studies of the validity of observed structured clinical exams have found low correlation with various written exams as well as with faculty evaluations. Since the United States Medical Licensing Examination (USMLE) results are often used by training programs in the selection of applicants, we assessed the correlation between performance on an observed structured clinical exam and the USMLE, steps 1 and 2, for internal medicine housestaff.
Methods: We collected scores on the USMLE, steps 1 and 2, and the overall score from a required standardized patient encounter for all PGY-1 trainees, in a single urban teaching hospital. Pearson coefficients were used to compare the USMLE and observed structured clinical exam performance.
Results: The two steps of the USMLE correlated with each other to a large extent (r=0.65, df=30, p=0.0001). However, both steps of the USMLE correlated poorly with the observed structured clinical exam (step 1 r=0.2, df=32, p=0.27; step 2 r=0.09, df=30, p=0.61).
Conclusions: The low correlation between the USMLE and performance on a structured clinical exam suggests that either the written exam is a poor predictor of actual clinical performance, the small window of clinical skills measured by the structured clinical exam is inadequate, or the two methods evaluate different skill sets entirely. Our findings are consistent with previous work finding low correlations between structured clinical exams and accepted common means of evaluation, such as faculty evaluations, other written exams and program director assessments. The medical education community needs to develop an objective, valid method of measuring important, yet subjective, skill-sets such as interpersonal communication, empathy and efficient data collection.
Key Words: Standardized patients, observed structured clinical examination, housestaff, United States Medical Licensing Examination (USMLE), performance.

Introduction

THERE IS INCREASING INTEREST in using "standardized patients" to assist in evaluating the clinical skills of residents, i.e., to reliably and validly measure history taking, physical examinations and interpersonal skills, which are difficult to measure on a written exam (1). More than a decade ago, the American Board of Internal Medicine (ABIM) discontinued the oral portion of the certifying exam and left assessment of actual clinical performance to the individual residency program directors. They, in turn, have employed several methods to fulfill this requirement, ranging from summation of individual faculty evaluations to formal observation of clinical exercises with patients. It is hoped that by offering a standardized format, there will be a reduction in the bias of non-standard faculty evaluations of differing clinical presentations (2–4).

This approach to evaluating clinical skills has now been used for several years to assess the clinical skills of international medical graduates (IMG) as a requirement for Educational Commission for Foreign Medical Graduates (ECFMG) certification, which is a prerequisite to medical training in the United States. Due in large measure to public support for such objective validations of clinical skills, a Clinical Skills Examination (CSE) will become a part of the licensing requirements for all US medical school graduates. Beginning with the class graduating in 2005, step two of the United States Medical Licensing Examination (USMLE) will include a written portion and an observed standardized clinical examination (OSCE) portion (5).

The perceived necessity of such an external measurement of clinical skills has grown out of concern that medical school faculty have not been assuring such skills, due to lack of direct observation of student performance and faculty members' varying abilities to detect deficiencies (5).

From the [1]Department of Medicine, Yale University School of Medicine, New Haven, CT, and [2]Department of Psychiatry, Albert Einstein School of Medicine, Bronx, NY and the Zucker Hillside Hospital, Glen Oaks, NY.

The work was done at the Department of Medicine, Maimonides Medical Center, Brooklyn, NY.

Address all correspondence to William Rifkin, M.D., Associate Director, Yale Primary Care Residency Program, Waterbury Hospital, 64 Robbins Street, Waterbury, CT 06721; email: wrifkin@wtbyhosp.chime.org

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Similar concerns have been raised at the Graduate Medical Education (GME) level as well. Specifically, suggestions to date have centered on closer day-to-day observation of patient care and incorporation of the ABIM's Clinical Evaluation Exercises (CEX and mini-CEX) (5–7).

Previous work has approximated the inter-rater reliability of so-called "standardized patients" (4, 8–9), with results ranging from 0.40 to 0.80. Other studies have examined the validity of performance on an observed structured clinical exercise using standardized patients by correlating performance with various so-called "gold standards." Correlations with overall program director assessment of intern performance, as well as summation of faculty evaluations ranged from 0.00 to 0.40 (2, 3). Written exams (in-training exam, ABIM written certifying exam, and its predecessor, the National Board of Medical Examiners Examination) correlated, with a range from 0.22 to 0.30 (2, 4). Correlations were more substantial between written exams, for example, between the in-training exam taken during postgraduate year-2 (PGY-2) and PGY-3 years and the ABIM exam results (0.59 and 0.68, respectively) (10). Previous work found that USMLE step one (0.16) and step two (0.30) correlated modestly with fourth-year medical student performance on an observed structured clinical exam (11).

We assessed whether performance with standardized patients correlates with USMLE scores for PGY 1 internal medicine residents. To our knowledge, this has not been done previously. The result of the study may be of interest especially to program directors, since the USMLE is often used as a major criterion for housestaff selection in the United States (12).

Methods

We collected scores on the USMLE, steps one (basic science) and two (clinical science), and the overall score from a required standardized patient encounter for all PGY-1 internal medicine housestaff at an urban tertiary-care community teaching hospital, over two years (2001 and 2002). First attempt USMLE results for each part were used in the case of multiple attempts. The standardized patient encounter was administered in the fall of the intern year. Each physician was scored in three domains (history taking, physical examination and interpersonal skills) while assessing four actor-patients portraying the following: obesity, shortness of breath, sickle cell disease and abdominal pain. Stated inter-rater reliability for this exercise was 0.49 in 2002 and 0.62 in 2001 (13). We used Pearson correlation coefficients to compare steps one and two of the USMLE and the standardized patient exam. There was no external funding provided.

Results

We had 32 pairs of scores available for comparison between the two steps of the USMLE and between step two and the standardized patient exam. We had 34 pairs of scores available for comparison between step one and the standardized patient exam. As expected, the two steps of the USMLE correlate to each other to a large extent ($r = 0.65$, $df = 30$, $p = 0.0001$). But we found that the standardized patient exam correlates poorly with both steps of the USMLE. The relationship to step one ($r = 0.20$, $df = 32$, $p = 0.27$) accounts for only 4% of the variance. The relationship to step two is even less than to step one ($r = 0.09$, $df = 30$, $p = .061$), accounting for only 0.8% of the variance.

Discussion

The very low correlation found between the United States Medical Licensing Examination and performance on the observed structured clinical exam suggests that either the USMLE is a poor predictor of actual clinical performance, or conversely, that the small window of clinical skills measured by the standardized patient exam affords little ability to discriminate. It was surprising to find that step two of the USMLE, the clinical knowledge section, was not more highly correlated than was step one, the basic science section. And why step one correlated more closely than did step two is not clear. It is possible that this variation was due to chance, that is, the observed differences between step one and two were not significant or meaningful. We could speculate that some aspect of the particular OSCE employed or the population examined, mostly IMGs, could account for this finding. To examine this, we tested the null hypothesis that the step 1 and step 2 correlations to the clinical exam are not different. Our results ($z=0.4354$, $p=0.33$) confirmed this; thus we are unable to conclude that the correlations are indeed different. We therefore conclude that neither step of the USMLE predicts performance on the OSCE.

Some investigators who also found low correlations between standardized patient tests and other forms of evaluation (program director assessments, faculty evaluations, written examinations) suggested that this demonstrates that the different evaluations assess different skills, citing this as an advantage (1, 9, 11).

An assessment demonstrates its usefulness by predicting an important outcome. One of the assessments with which the observed structured clinical exam correlated poorly in this study (basic science written exam scores) does predict obtaining ABIM certification (14). Therefore, does the observed structured clinical exam provide useful predictions? This remains to be demonstrated. To do so requires a "gold standard" for good clinical skills, and it is unlikely that one such standard will ever appear. Perhaps the optimal procedure involves cross-correlation of several assessments with high face validity, such as real-time faculty or peer assessments.

Limitations of this study include the fact that our sample included many non-US-citizen international medical graduates (45%) and US-citizen international medical graduates (25%), who may not be representative of programs nationwide. In addition, our sample was drawn from a single residency program and may not be replicated in larger, more geographically diverse samples. It should also be noted that while the USMLE steps were taken in medical school, the OSCE was taken during internship, that is, at two distinct phases in medical education. It is possible that some of the variation found could be due to aspects of training incorporated during the latter part of medical school or during the internship itself. However, this would not detract from our conclusion that the USMLE itself is a poor predictor of the OSCE performance and perhaps then more generally of clinical performance, if one presumes that OSCE performance should predict performance in true clinical practice.

In conclusion, brief observations of patient assessments should be tested against a measure of clinical competence that has proven validity. That is, the medical education community needs to develop and test an objective method of measuring important, yet subjective skill-sets such as history-taking, physical examination and interpersonal skills.

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Malignant Fibrous Histiocytoma of the Liver:

A Case Report and Review of the Literature

George Anagnostopoulos, M.D.[1], George H. Sakorafas, M.D.[2],
Kyriakos Grigoriadis, M.D.[3], and Panagiotis Kostopoulos, M.D.[1]

Abstract

Malignant fibrous histiocytoma (MFH) is a common soft tissue sarcoma, usually occurring in the extremities. MFH of the liver is an extremely rare neoplasm, with only 28 cases reported in the international literature since 1985. We present a case of MFH of the liver in an 87-year-old woman. The tumor was located in the right lobe of the liver and measured 12 × 8 cm. It consisted of spindle-shaped, pleomorphic, malignant cells in a storiform pattern associated with histiocyte-like cells and giant cells. Most of the tumor cells and giant cells were vimentin and α_1-antichymotrypsin positive. Histopathological findings were consistent with an MFH of the storiform / pleomorphic subtype. The literature is briefly reviewed.

Key Words: Histiocytoma, liver, sarcoma.

Introduction

Malignant fibrous histiocytoma (MFH) represents the most common soft tissue sarcoma in adults (1). It can occur almost everywhere, owing to its mesenchymal origin (2, 3). However, its origination in the liver is extremely rare, with only a few cases reported in the literature. A case of an MFH of the liver is presented and the literature is briefly reviewed.

Case Report

An 87-year-old woman was admitted to our hospital for evaluation of progressive weight loss of 15 kg (33 lbs) in 6 months, right upper quadrant pain, and low-grade fever. The patient denied any history of abdominal trauma, blood transfusions, or alcohol intake. Physical examination revealed a non-icteric woman with a temperature of 37.7°C. Abdominal examination revealed tenderness in the right upper quadrant of the abdomen, while the liver was palpable 7 cm below the right costal margin. Chest X-ray showed an elevated right hemidiaphragm. Erythrocyte sedimentation rate was 112 mm/h, hematocrit 34.2%, white blood cell count 13,700 cells/mm^3, and platelet count 617,000/mm^3. Total serum protein, electrolytes, creatinine, glucose, transaminases, alkaline phosphatase and bilirubin were within normal limits. Fibrinogen was elevated (478 mg/dL), as was lactate dehydrogenase (1652 IU/L). Test results for carcinoembryonic antigen (CEA), α-fetoprotein (a-FP), 19-9 carbohydrate antigenic determinant (CA 19-9), and hepatic viral markers were all negative.

Abdominal ultrasound revealed a large mass localized in the right lobe of the liver. Abdominal computerized tomography (CT), after bolus intravenous injection of contrast medium, confirmed the presence of a large, hypodense intrahepatic mass (12 × 8 cm) in the right hepatic lobe (Fig. 1). There was no evidence of adenopathy or retroperitoneal masses, and the pancreas was normal.

CT-guided biopsy of a solid portion of the tumor yielded spindle-shaped, pleomorphic, malignant cells arranged in sheets and fascicles with a prominent storiform pattern (Fig. 2). Numerous histiocyte-like

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From the Departments of [1]Gastroenterology, [2]Surgery, and [3]Pathology, 251 Hellenic Air Force (HAF) Hospital, Athens, Greece.

Address all correspondence to George H. Sakorafas, M.D., Arkadias 19 – 21, GR-115 26 Athens, Greece; email: georgesakorafas@yahoo.com

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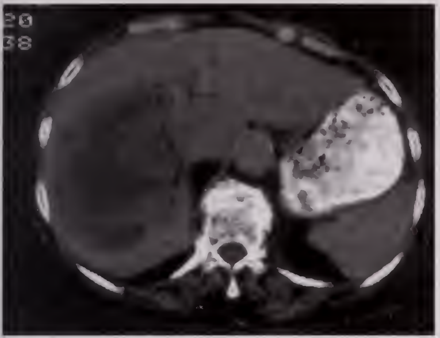

Fig. 1. Abdominal CT scan showing a large hypodense mass involving almost the entire portion of the right liver lobe.

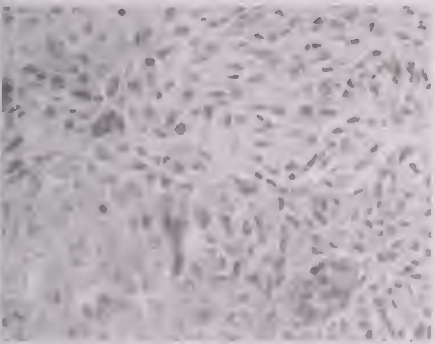

Fig. 2. Histology revealing the presence of pleomorphic spindle cells arranged in sheets and fascicles with a prominent storiform pattern (H&E, × 400).

cells and giant cells were observed. Immunohistochemistry showed that the tumor cells and most of the giant cells and histiocyte-like cells were vimentin-positive (Fig. 3). Most of the tumor cells, including giant cells, were also cytoplasm positive for α_1-antichymotrypsin. The histopathologic findings were consistent with an MFH of the storiform-pleomorphic type. Because of the large size of the tumor, the advanced age of the patient, and the presence of significant comorbidity, the tumor was judged to be inoperable. The patient died six months after diagnosis.

Discussion

MFH is a common soft tissue sarcoma. It usually occurs in the extremities, presenting as a painless mass, and less commonly in the retroperitoneal space, presenting with weight loss and increased intra-abdominal pressure (1). Since its initial description in 1963 (2), MFH has remained a rare neoplasm of uncertain histogenesis. It is thought to originate from undifferentiated mesenchymal cells, which are capable of multidirectional differentiation; this may explain why it has the potential to be found in all organs (3). Five histologic subtypes of MFH have been described: pleomorphic storiform (65% of cases), myxoid (15%), giant cell (10%), inflammatory (8%), and angiomatoid (2%). The first two subtypes tend to be high-grade neoplasms, while the others are usually low-grade sarcomas (1). The differential diagnosis of MFH should include pleomorphic liposarcoma and rhabdomyosarcoma. The former lacks the storiform pattern and shows evidence of cellular differentiation, while the latter shows cross striations on histologic examination. Weiss and Einzinger analyzed 200 cases of MFH (1) and showed that the 2-year survival rate of patients with pleomorphic / storiform type of MFH was 60% and the rate of metastases was 42%. Tumors larger than 10 cm had a rate of metastases of 57%, while those with a diameter from 5 – 10 cm, 34%. Surgery is the only effective method of treatment of MFH. Chemotherapy and radiotherapy have been used, but without success.

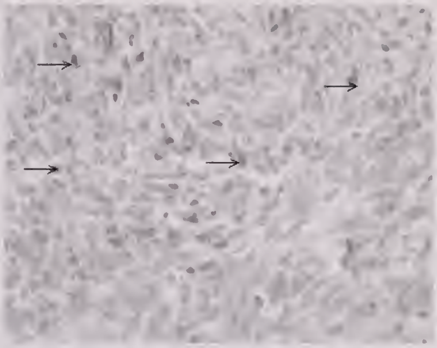

Fig. 3. Cytoplasmic immunoreactivity for vimentin was present in most tumor cells (see arrows, showing some of these cells) (immunoperoxidase stain, × 100).

Primary MFH of the liver is very rare. It was first reported in 1985 (4), and since then only 28 other cases have been reported in the international literature (4 – 19) (16 men, 12 women, age range: 27 – 79 years, mean age: 51 years). Mean diameter of the tumor was 12 cm, with no predilection for one lobe or the other as the origin site. In 11 cases there was direct invasion of the adjacent organs; in only 2 cases were there distant metastases in the lungs. Most of the MFHs were pleomorphic; only two myxoid and one inflammatory type have been reported. In our patient, the MFH was the storiform / pleomorphic type, and immunohistochemically most tumor cells expressed vimentin and α_1-antichymotrypsin. There was no evidence of metastatic disease at the time of diagnosis.

Most of the patients reported in the literature were treated surgically, but prognosis was poor. With a mean follow-up of 48 months, only 7 patients survived following surgery without any evidence of local recurrence or distant metastasis.

Modern imaging modalities (ultrasonography, CT) typically reveal a well-defined, large hepatic mass, with variable hemorrhagic necrosis, and invasion of the liver capsule or even tumoral spread to adjacent organs, without intratumoral calcification or regional lymph node metastasis. There is no specific imaging difference between hepatic MFH and MFH arising in other organs, but dystrophic calcification and metaplastic ossification—which is frequently reported in retroperitoneal and musculoskeletal MFH—has not been described in any case of hepatic MFH.

In conclusion, MFH of the liver is an extremely rare neoplasm with an aggressive biological behavior; it should be considered in the differential diagnosis of large liver lesions.

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Abstracts

Participation in Medical Student Research Day continues to grow. This year we had 82 participants. The scope and depth of the projects done by MSSM students are impressive. New mentors are participating every year, offering our students the chance to do research in a wide variety of areas. Student efforts translate into a very special educational experience. According to official surveys, MSSM has far more students than the national mean who do research and more students than the national mean who coauthor manuscripts. I would like to thank Dean Kenneth Davis and Dean of Medical Education Larry Smith for their continued support of medical student research, and acknowledge Grace Oluoch, Annabelle Rinaldo, Michelle Sainte, and the MSSM Alumni Association.

Karen Zeir, Ph.D.
Associate Dean for Medical Student Research

Tenth Annual Medical Student Research Day

November 12, 2004

The Role of Pre-synaptic Active Zone Proteins in the Development of Opiate Addiction. N.S. Abul-Husn, J.A. Morón, and L. Devi. Department of Pharmacology and Biological Chemistry, Mount Sinai School of Medicine, New York, NY.

An important characteristic of opiates is their capacity to induce compulsive drug-seeking behavior, a major component of drug addiction. Despite extensive research in this field, the molecular mechanisms underlying the development of opiate addiction remain poorly understood. Opiates, such as morphine, are known to act on both pre-synaptic and post-synaptic receptors to produce their neuronal effects. They regulate a spectrum of signaling molecules, including serine/threonine kinases such as mitogen-activated protein kinase (MAPK), protein kinase Cg (PKCg), and calcium/calmodulin-dependent kinase (CAMK) II. To date, very little attention has been given to the influence of pre-synaptic signaling molecules in the development of opiate addiction. This is partly due to a prior inability to effectively isolate and characterize the pre-synaptic active zone (PAZ). In this study, we have used a novel approach to isolate the PAZ from mouse brains in high yield and purity. We have determined that several signaling molecules known to be involved in opiate signaling are associated with the PAZ. We are currently exploring the changes in expression and activation of these PAZ proteins during morphine addiction, using a proteomics approach. These studies will lay the foundation for a better understanding of the pathways involved in opiate addiction and are a prerequisite to the development of novel therapies for the treatment of narcotic addiction.

Complementary Alternative Medicine Use in Older Adults in East Harlem. K.A. Artis, S. Hu, C.X. Pan, and J.L. Howe. Departments of Geriatrics and Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Complementary alternative medicine (CAM), defined as a group of medical practices that do not conform with the standards of the medical community, includes modalities such as acupuncture, chiropractic and herbal supplements. CAM use is increasingly prevalent in older adults in the United States. While some research on geriatric CAM use exists, little is known about its use in ethnically diverse, low income and community-dwelling populations. Understanding geriatric CAM use in older adults is important because it may help prevent potentially harmful drug-herb interactions for which geriatric patients on complex medicine regimens are particularly at risk, as well as help provide patient-centered care. This study explored CAM use prevalence and characteristics among community-dwelling older adults in East Harlem, NY. On-site social service coordinators assisted in the recruitment of 100 participants who were interviewed in English, Spanish or Mandarin. The survey asked a series of questions about types of CAM used, reasons for use, referral sources, perceived efficacy and monthly expenditures. After adjusting the results to exclude prayer and commonly prescribed vitamins, analysis revealed that two-thirds of participants were CAM users and that participants living in Linkage House, and those not born in the United States, were more likely to use CAM. The primary information source about CAM came from the community, including family and friends. Only 1% of CAM users reported adverse events, while 81% reported high satisfaction with CAM. Health providers working with older populations should be aware of the high rate of CAM use among their patients and the implications of this phenomenon.

Assessment of the Gap between HIV/AIDS Treatment and Prevention in the Setting of a Traditional Siddha Organization in Tamil Nadu, India. K. Baban, S. Ikeda, N. Hennig, MD/PhD, D. Pooran, and H. Sacks, MD/PhD. Thomas C. Chalmers Clinical Trials Unit, Mount Sinai School of Medicine, New York, NY.

Gandeepam is a non-governmental organization in the poor south Indian state of Tamil Nadu. In a country with one of the most rapidly increasing rates of HIV infection, the small state of Tamil Nadu contains close to 50% of India's cases. Gandeepam practices Siddha medicine, an affordable traditional healing method, and focuses on the curative treatment of HIV/AIDS. As part of a network of 60 Tamil Nadu NGOs (the Gandeepam Global Foundation, GGF), Gandeepam's presence in the community also extends far beyond the medical, providing after-school tutoring, organizing financial empowerment groups, and more. The purpose of this assessment is to determine whether Gandeepam and its partners make maximum use of the tremendous opportunities thus provided to promote HIV awareness, prevention, and treatment. The gap that keeps treatment discrete from education and prevention is a global phenomenon, acknowledged as a major challenge to controlling the spread of HIV/AIDS. Three weeks with Gandeepam, and survey responses from 39 GGF NGOs, yielded widely varied approaches to HIV/AIDS education and prevention, and no discernible coordination with treatment. Among other findings: Most GGF NGOs, including Gandeepam, neither provide, promote, nor believe in condoms to prevent HIV transmission. Reluctant to discuss such issues with men or single women, those that do promote condoms usually target married women. A minority of GGF organizations provides condoms to sex workers. Compounding these issues, Gandeepam considers treated patients cured and thus does not advise on how to prevent transmission. This preliminary assessment shows great potential but also tremendous social obstacles to the dissemination of effective education and prevention messages, and perhaps offers insight into challenges faced globally.

Increased Body Mass Index (BMI) and Psychosocial Dysfunction in Children: Is There an Association? T.M. Balija and D. Steinbaum. Department of Pediatrics, Mount Sinai School of Medicine, New York, NY.

Obesity and mental health disorders have been shown to have a co-morbid relationship in adult populations. Currently, there is a paucity of literature examining this association in inner-city school-age populations. Among adults living in New York City, East Harlem is the epicenter of both obesity and mental illness. This community has several socioeconomic factors that contribute to both the high prevalence of mental health diagnoses and obesity experienced by its residents. As part of an ongoing research study at the Pediatric Associates Practice of the Mount Sinai School of Medicine, this study will examine the relationship between body mass index (BMI) and psychosocial dysfunction in the 8- to 10-year-old patients of an East Harlem pediatric clinic. Psychosocial dysfunction will be determined using the Pediatric Symptom Checklist (PSC), an accepted screening tool, and BMI will be determined via chart review. This study hypothesizes that BMI and PSC scores will be directly correlated: i.e. as PSC scores increase, BMI increases. It is intended that findings from this study will inform physician management of concurrent obesity and mental health problems.

Immunohistochemical Analysis of Caspase-3 in G86R Superoxide Dismutase-1 Transgenic Mice. M.A. Barnes[1], W.G.M. Janssen[2], J.H. Morrison[2], and D.J. Lange[1]. [1]Department of Neurology, and [2]Fishberg Department of Neuroscience, Mount Sinai School of Medicine, New York, NY.

Purpose: To establish the localization of caspase-3 in both its inactive and active forms in the G86R SOD-1 transgenic mouse, a valuable model of ALS.

Methods: Fluorescent immunohistochemistry established localization of inactive caspase-3 (CPP32),SOD-1,ChAT and active caspase-3.

Results: Non-transgenic and transgenic mice expressed SOD-1 cytoplasmically. The transgenic mouse motor neurons showed intense cytoplasmic localization, apoptotic morphology and nuclear membrane breakdown. SOD-1 cytoplasmic expression in non-transgenic mice was low and the motor neuron morphology was normal. In both groups CPP32 showed nuclear localization. The non-transgenic mice showed a bright nuclear signal, whereas the transgenic mice had a weaker nuclear signal. Activated caspase-3 was intensely cytoplasmic in the transgenic mice, while only a couple of cells, in the non-transgenic mice showed weak cytoplasmic localization. Staining with ChAT of motor neuron populations identified a relative decrease in transgenic mice.

Conclusions: The role of SOD-1 in ALS pathogenesis is still unclear; however, there is a different pattern of expression in transgenic and non-transgenic mice. The low levels of CPP32 coupled with the high levels of active caspase-3 in transgenic mice may represent the transformation and translocation of inactive caspase-3 into overexpressed active caspase-3. The loss of motor neurons, identified by the localization of ChAT validates the notion that symptomatic transgenic mice lose motor neurons. Our data supports the hypothesis that caspase-3 activation is an integral part of the process responsible for motor neuron loss in ALS.

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Internodal Conduction Pathways in the Adult Mouse Atria. E.L. Baron, K.J Casey, and G.E. Morley. Department of Medicine, Division of Cardiology, New York University School of Medicine, New York, NY.

Atrial fibrillation, the major cardiac cause of stroke, is the most common sustained cardiac arrhythmia. Three atrial structures, crista terminalis, Bachmann's bundle, and the Eustachian valve, have been identified as morphologically crucial in understanding the internodal pathways of the human heart. It is widely accepted that these structures contribute to the complex patterns of propagation during atrial arrhythmias. We hypothesize that the heterogeneous anatomical and electrophysiological properties of the murine atria interact to coordinate electrical activation. High resolution optical mapping of voltage dye fluorescence was used to study patterns of atrial excitation in isolated Langendorff-perfused murine hearts. Activation maps were generated showing the spread of electrica excitation. Following imaging studies, hearts were paraffin-embedded and sectioned at 10um. Images of sections will be used for 3D reconstruction of hearts onto which activation maps will be superimposed. Initial mapping studies have identified the location of the SA node on the posterior upper right atrium, at the junction of the superior vena cava and crista terminalis. The signal spreads rapidly and anisotropically from the SA node through the right atria, presumably via the posterior internoda pathway. Slower conduction was observed as the wavefront moved toward Bachmann's bundle presumably via the anterior pathway. Thus, we have demonstrated electrical heterogeneity within the mouse atria. Our conduction patterns correspond well with previously described morphological internodal pathways. Ongoing studies in the laboratory involve 3D visualization of internodal pathways, and determining the role of intercellular coupling in establishing and maintaining atrial conduction between the SA and AV nodes.

Effect of Cardiac Catheterization on Left Ventricular Compliance. A Belanger, M. Chiu, L. Croft, MD, and M.E. Goldman, MD. Department of Cardiology, Mount Sinai Hospital, New York, NY.

Cardiac catheterization (cc) is an invasive therapeutic and diagnostic exam of the coronary vessels. While focused on coronary patency and improving systolic function, the impact of the >800,000 annual caths on LV diastolic function has not been well studied. Therefore, we recruited twenty-three consecutive consenting patients undergoing a cc procedure We performed limited 2-D Doppler echoes prior to and 2 – 24 hours following cc, using the transmitral E/A ratio as a measure of LV compliance (E/A >1 suggests a compliant LV, while E/A <1 suggests a stiff LV). Of the 23 patients studied, 16 underwent stenting and had a significant decrease in E/A (–0.16) compared to those without stenting (n=7, 0.01 (p=0.021). Interestingly, first time catheterization patients' E/A ratios decreased (improved) an average of 0.051 while patients with at least 1 prior cath increased (worsened) an average of 0.191 (p=0.013). While this preliminary study was too small to assess all variables, it is the first to suggest that intervention such as stenting during cc may impact LV diastolic compliance, which may indicate damage to small vessels.

The Effect on Lifespan of Ablating Isocitrate Dehydrogenase 2 in Eat 2 Mutants of C. elegans. R.E. Berger, K. Yen, and C.V. Mobbs. Fishberg Research Center for Neurobiology, Mount Sinai School of Medicine, New York, NY.

Caloric restriction increases lifespan and is thought to retard the aging process. Eat 2 mutants of *C. elegans* have a pharyngeal defect that approximates caloric restriction. Our group has shown that caloric restriction induces isocitrate dehydrogenase 2, an enzyme that is thought to play a major role in anti-oxidant defenses by producing NADPH in the mitochondria. Jo et al. state, "Decreased expression of isocitrate dehydrogenase 2 markedly elevates the ROS generation, DNA fragmentation, lipid peroxidation, and concurrent mitochondrial damage with a significant reduction in ATP level." We hypothesized that caloric restriction increases lifespan in part by inducing isocitrate dehydrogenase 2. We therefore assessed whether inhibiting the synthesis of isocitrate dehydrogenase 2 would block the effects of caloric restriction to increase lifespan. Using RNAi, we ablated isocitrate dehydrogenase 2. At day ten of our study, ablation of isocitrate dehydrogenase 2 had no effect on survival in non-calorically restricted control worms. In contrast, ablation of the isocitrate dehydrogenase 2 gene significantly reduced the effect of the Eat 2 mutation to increase lifespan. This result suggests that isocitrate dehydrogenase 2 expression may play a key role in the life-extending effect of Eat 2 induced caloric restriction.

Premenstrual Dysphoric Disorder: Physicians' Perspectives. E.J. Bernstein, and D.R. Korenstein, MD. Division of General Internal Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Premenstrual Dysphoric Disorder (PMDD) recently entered the DSM-IV without an official category or axis. This project investigates physicians' diagnostic and prescription behaviors surrounding PMDD: how they distinguish it from PMS and prescribe SSRI's for its treatment; and the level of information they provide when prescribing Sarafem (fluoxetine). Whether physicians accept this diagnosis will ultimately affect its utility. I hypothesize that physicians' employment of this diagnosis correlates with their prescription behaviors. At stake is the role of the pharmaceutical industry in influencing physician diagnostic behavior. Seventy-seven Mount Sinai physicians in the departments of OB/GYN, Medicine, Psychiatry, and Adolescent Medicine completed an on-line survey. Fifty-seven see women of reproductive age; their responses were included in the analysis. Structured interviews were conducted with twenty respondents. The results indicate little consensus surrounding the diagnosis and treatment of PMDD. Thirty-nine percent of participants define PMDD as more severe than PMS; 19% make no distinction. Eighteen percent characterize PMS by physical symptoms and PMDD by mood/psychological symptoms. Forty-seven percent of respondents instruct patients to take SSRI's during the luteal phase only; 34% instruct patients to take SSRI's daily. The pharmaceutical industry's influence is apparent: 49% of respondents prescribe Sarafem for PMDD, 96% of whom inform women that Sarafem is identical to Prozac. Moreover, 32% of respondents had patients request Sarafem. Given the disagreement surrounding the diagnosis and treatment of PMDD, research is needed about the physiological basis of PMDD, the differences (if any) between PMDD and PMS, and the mechanism of action of SSRI's for the treatment of PMDD when only taken during the luteal phase.

East Harlem Pediatric Asthma: Parent/Child Diad Disparities in Awareness of Psychological Toll. P.W. Burke, T.I. Evtimova, and E.J. Garland. Department of Community and Preventive Medicine, Healthy Families Healthy Community Program, Mount Sinai School of Medicine, New York, NY.

Background: East Harlem continues as the neighborhood most afflicted by pediatric asthma in all of New York City's boroughs, with 17.55 hospitalizations per 1000 children, ages 0–14 years. This starkly contrasts to the 6.91 hospitalizations per 1000 children for Manhattan as a whole in the same age group. Furthermore, an April 2003 study by the New York City Department of Health and Mental Hygiene revealed approximately 30% of East Harlem children will suffer from asthma at some time during their lives. Little is known, however, regarding how pediatric asthma affects East Harlem children psychologically. Therefore, this project evaluates (a) pediatric asthma's psychological toll on patient quality of life and (b) parental awareness of this psychological toll.

Methods: Psychological impact and parental cognizance of the degree and extent of pediatric asthma's psychological effect were assessed by an original, standard 22-question verbal interview administered to East Harlem children and their respective parents.

Results: Statistical analysis of data, rendered on a Likert scale of four, includes individual examination of school performance effects, psychological outlooks, activity limitations/quality of life, social ramifications, and medical care efficacy while also performing paired T-tests to evaluate significant disparities between each parent/child diad's replies.

Conclusion: Disparities and differences shall be further explored, with an eye towards possible future education and fostering better parent-child communication and adult empathy regarding pediatric asthma.

Effects of Time Since First Depressive Episode on Cognition in Patients with Recurrent Major Depressive Disorder. C.M. Celano, M.A. Rapp, A. Reichenberg, K. Dahlman, and J.M. Gorman. Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Background: Recently, decreased hippocampal neurogenesis has been proposed in major depressive disorder (MDD). At the same time, hippocampal volume loss has been associated with longstanding MDD, and patients with recurrent geriatric MDD have been shown to have distinct deficits in delayed recall. However, few studies have examined the effects of depression duration on neuropsychological performance, and they have yielded inconsistent results. The aim of our study was to determine the effects of the amount of time since first depressive episode in patients with recurrent MDD on 5 cognitive domains: short- and long-term memory, fluency, attention, and visuospatial learning.

Methods: The neuropsychological evaluations of 59 adults with recurrent MDD were examined. For each participant, the year of first episode of MDD was recorded. Pearson correlations, partial correlations, and regression analyses assessing the association between years since first episode of depression and neuropsychological variables were performed.

Results: A moderate (r=–0.377) negative correlation was found between years since first episode of depression and the delayed recall cognitive domain, controlling for the effects of age. Regression analyses indicated that, beyond age, gender and education, years since first episode of depression had a significant effect on delayed recall in our sample.

Conclusions: These results suggest that suffering from recurrent MDD for a long period of time may result in the specific impairment of long-term memory, possibly related to hippocampal dysfunction. These results may explain distinct deficits in recall observed in recurrent geriatric MDD.

The Role of B4 Integrin in Squamous Cell Carcinomas. P.R. Chaudhari, B.A. Horst, and M.P. Marinkovich. Department of Dermatology, Stanford University, Stanford, CA.

Squamous cell carcinoma (SCC) is one of the most common tumors with an incidence of 80 in 100,000 people per year. In a recently described tumor model, normal keratinocytes can be transformed into SCC-like cells via overexpression of Ras and IkBa. Formation of tumors in this model has been shown to be dependent on expression of a6b4 integrin and laminin 5. Integrins are transmembrane receptors essential for attachment and interaction of keratinocytes with the ECM. In order to further define the role of the a6b4 integrin, mutant forms of b4 integrin which cannot bind to extra and intracellular ligands, are re-expressed in keratinocytes. These studies are critical in defining the mechanism of the formation of SCC. Overexpression of Ras and IkBa is achieved by retroviral transfer of these genes into keratinocytes with stable integration into the genome. Using a fibroblast packaging cell line, viral supernatant for infection with Ras and IkBa was produced and tested on normal keratinocytes. Overexpression of both Ras and IkBa protein was confirmed by Western blot. The viral titer will be further used to transform keratinocytes expressing mutant forms of b4 integrin into SCC-like cells to test their tumor forming potential. Preliminary results suggest that the interaction of a6b4 integrin with laminin 5 is essential for this process. A mutant form of a6b4 integrin has been found to significantly inhibit tumor formation in this model. Further insight into the interactions may ultimately lead to development of new drugs for targeting early stage squamous cell carcinoma.

The Perception and Evolution of Medical Error in the Health Care Profession and Consequential Impact on Education of Physicians. P.W. Chen, D. Muller, and K. Ornstein. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

The lay press and the medical literature have extensively covered many aspects of medical errors: from data on their frequency and outcomes, to suggestions for reducing error, to attempts at understanding how errors should be handled. As medical trainees develop a tolerance over time to pain, suffering, tragedy, we believe that they develop a tolerance to errors. Our hypothesis is that the perception and definition of a medical error undergoes a transformation or evolution in the minds of most trainees over the course of their transition from students to residents. Through pilot studies (phase 1) and previously collected surveys (phase 2) distributed to all first year entering students, third year medical students after they have completed their clinical clerkships, medical interns at the end of internship, and graduating third year medical residents, we hope to continue the project this summer by showing a dramatic difference between the perceptions of incoming first year students and graduating house staff through extensive data compilation and analysis (phase 3). We also expect that, with some variation, there will be a graded change in perception over time. Students who have not had clinical experiences will define errors more broadly and will be harder on themselves for errors they make. Residents will define error more narrowly and will be more adept at minimizing their personal and professional fallout. We hope to gain a better understanding of how the perception of medical error evolves during critical phases of medical training, and more specifically what factors influence this evolution.

Does FAK Control Fibroblast Migration by Regulating the Localization of ZO-1 to Lamellipodia? A.S. Chheda, M. Benezra, and S.K. Masur. Ophthalmology, Mount Sinai School of Medicine, New York, NY.

ZO-1is an intracellular protein component of tight junctions, and has been shown by our lab to localize to the leading edge of lamellipodia of migrating corneal fibroblasts in a cell culture model of wounding. The possibility that lamellipodial ZO-1 plays a role in migration was suggested by preliminary studies of mouse embyonic fibroblasts lacking FAK (focal adhesion kinase): FAK-/- cells have inhibited migration and they also lack lamellipodial ZO-1. To test whether the absence of FAK is responsible for the decrease in lamellipodial ZO-1, we decreased FAK in two other ways: (a) transfecting FAK siRNA to prevent the transcription of FAK mRNA and (b) transfecting GFP tagged-FRNK, a dominant negative for FAK kinase activity. si RNA, or GRP-FRNK or appropriate controls were introduced into mouse embryonic fibroblast . After 3 days, we fixed and immunodetected FAK and ZO-1. Both FRNK cells and siRNA cells had decreased expression of FAK in their focal adhesions. Furthermore, less ZO-1 was detected in their lamellipodia and cell-cell contacts. We plan to do migration studies to test the hypothesis that decreased lamellipodial ZO-1, decreases migration. The results of this study support a role for FAK kinase cascade in regulation of ZO-1 in cell junction formation and possibly for fibroblast motility in the wound healing process. This information would afford us a more complete understanding of the factors that mediate corneal wound healing, which can help us to avoid the complications of slowed and impaired wound healing as in infections and blindness.

Acute Impact of Cardiac Catheterization on Ischemic Mitral Regurgitation and Left Ventricular Wall Motion. M. Chiu, A. Belanger, L. Croft, MD, and M.E. Goldman MD. Department of Medicine/Cardiology, Mount Sinai Hospital, New York, NY.

Though ischemic mitral regurgitation (MR) is often indirectly addressed with percutaneous revascularization, with the expectation that treating the underlying coronary artery disease (CAD) will lead to its eventual resolution, there have been no "acute" studies. To determine the immediate impact of catheterization on ischemic MR on left ventricular wall motion, we recruited 35 consecutive consenting patients and performed a pre-catheterization echocardiogram focusing on the left ventricular wall motion and the presence and severity of MR (graded on a scale of 0–4). A second echocardiogram was performed 2–24 hours following the catheterization procedure on 28 patients. Fifteen of the 35 patients (43%) had at least mild MR with 9 of 35 (25%) classified as ischemic MR. Three of 7 (43%) interventional ischemic MR patients displayed marked MR improvement (defined as a decrease of > one grade) while neither of the two non-intervention ischemic MR patients displayed marked improvement. In addition, 8 of 17 intervention patients (47%) displayed an improvement in wall motion in at least one left ventricular segment, while there were no changes in wall motion in any non-intervention patients. Two intervention patients displayed deterioration in at least one segment. While our study is too small to draw any broad conclusions, our preliminary findings suggest that revascularization of the left ventricle results in acutely improved wall motion and ischemic MR.

Is the TIMI Risk Score Predictive of Positive Stress Tests in Emergency Department Chest Pain Patients? E. Cho and L. Hermann, MD. Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Cardiac ischemia, a disease process associated with significant patient morbidity and mortality, is often difficult to diagnose at the time of initial presentation. Published data suggests 2–4% of patients with cardiac ischemia are inadvertently discharged from emergency departments each year. Recently, clinical risk scores have been developed to help guide therapeutic decisions regarding patients treated for possible cardiac ischemia. The TIMI risk score has been validated as a tool for establishing risk of death, myocardial infarct, or recurrent ischemia in high-risk chest pain patients but has not been applied to low-risk groups. The present study investigates whether the TIMI risk score can be applied to low-risk chest pain patients to help predict the presence of cardiac ischemia as demonstrated by a positive stress test. Patients presenting to the emergency department (ED) with symptoms of cardiac ischemia during the study period were screened for risk of complications via a validated protocol. Patients at low risk for complications were admitted to the ED ches pain unit (CPU) where they underwent serial EKG and cardiac enzyme testing to screen for myocardial injury. If negative, the patient then underwent a stress test to determine the presence of reversible myocardia ischemia. Patient records were accessed retrospectively using the electronic data system in the Mount Sinai ED. During the study period, 16 patients were evaluated in the CPU. A TIMI score was calculated for each patient. The scores ranged from 0–5, the lowest and highest possible score being 0 and 7, respectively. A score of 3 or higher indicates a moderate to high risk of cardiac complications. Data was analyzed using the Spearman Rank-Order Correlation Coefficient. Results showed no correlation between the TIMI score and the likelihood of a positive stress tes in patients (.064 correlation coefficient). Of the 142 patients classified as low risk (TIMI risk score 0–2), 15% had a positive stress test. This study shows that the TIMI risk score is not helpful in predicting the presence o cardiac ischemia in low to moderate risk patients.

Development of a Questionnaire to Measure Quality of Life in Families with a Food-Allergic Child: The Food Allergy Quality of Life–Parental Burden (FAQL-PB) Questionnaire. B.L. Cohen, S. Noone, A Muñoz-Furlong, and S.H. Sicherer. The Elliot and Roslyn Jaffe Food Allergy Institute, Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY.

Background: Food allergy is potentially severe, affects approximately 5% of children, and requires numerous measures for food avoidance to maintain health. The impact of this disease on health-related quality of life (HRQL) has been documented using generic instruments, but no disease-specific instrument is available.

Objective: To create a validated, food allergy-specific HRQL instrument to measure parental burden associated with having a food-allergic child.

Methods: After identification of 74 items affecting families with food allergic children, 88 families were approached for impact scoring Final items were generated by score results, elimination of redundancies and content review. Resulting high impact areas were queried for validation with a 7-point Likert scale. A final instrument including 17 items and 2 "Expectation of Outcome" questions was distributed to 352 families for validation.

Results: Areas of impact included: Family/social activities, restaurant meals, social activities, childcare, vacation, school, time for mea preparation, health concerns and emotional issues. Validation steps showed strong internal validity Cronbach α, 0.95 and good correlation with "Expectation of Outcome" questions $r=0.412$, $p<0.01$ and scores on a generic HRQL instrument, the CHQ-PF50 $r=-0.36$ to -0.4, $p<0.01$. The instrument showed the ability to discriminate by disease burden: parents whose children had multiple >2 food allergies were more impacted than those whose children had fewer allergies scores 3.1 vs. 2.6, $p<0.001$.

Conclusions: The FAQL-PB demonstrates strong internal and cross-sectional validity. Its discriminative ability suggests it will be a useful too to measure outcomes in treatment studies of food allergy for children.

Histological Analysis of Age and Gender-Related Changes in Endosteal, Intracortical, and Periosteal Porosity of the Distal Radius M.A. Cordova, J.W. Williams, D.C. Casagrande, J.E. Bird, D.M. Laudier C.J. Terranova, and K.J. Jepsen. Leni and Peter W. May Department of Orthopaedics, Mount Sinai School of Medicine, New York, NY.

Although bone density scans (DXA) are recommended to measure bone health at the hip, a peripheral site measurement would offer the advantage of minimizing central radiation exposure. However, the relationship between hip and wrist bone loss is not fully understood. This study's goa was to assess the bone loss progression of the distal radius as a function of age and gender. Bone loss was assessed from 44 cadavers (48–10 years; 24 females, 22 males). Total area (TA), cortical area (CA) medullary area (MA), and intracortical porosity (ICP) were quantified from digital images. The slopes of endosteal bone loss (MA/TA) and tota bone loss (MA+ICP)/TA versus age were two times greater in females compared to males. However, intracortical porosity (ICP/TA) increased with age for males but decreased for females. A high resolution analysis of the progressive increase in Haversian canal size from the periosteum to the endosteum revealed that individual pores increased in size and eventually coalesced subendosteally with neighboring expanding pores. The

ICP continued to increase until the size of the resulting pore ultimately coalesced with the marrow, leading to an age-related increase in MA and a decrease in ICP. Ongoing research will incorporate specimens of a younger population to view comparable trends over a broader age range. The results of this study provide new insight into age-related bone loss. Men and women show a similar pattern of bone loss; however, women tend to lose bone faster than men, perhaps contributing to the higher fracture incidence of fragility fractures in women.

Immune Assessment of Peripheral Blood Leukocytes. J. Corona, C.M. Divino[1], and S-H Chen[2]. [1]Department of Surgery and [2]Carl C. Icahn Center for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, NY.

Previous research has demonstrated that tumors often evade attack from the immune sytem due to defective immune cell function. Tumor-bearing cells secrete cytokines that affect cell proliferation causing atypical differentiation of the myeloid cell lineage causing an accumulation of immature myeloid cells (ImC). This population has been found to involve immune T tolerance and T regulatory cell development in murine tumor models. This study aimed to identify and quantify the abnormal cell populations present in the peripheral blood mononuclear cells (PBMC) of patients with cancer. Peripheral blood samples from both normal volunteers and cancer patients were obtained and assayed for the presence of ImC composed of immature monocytes, early stage myeloid and dendritic cells. PBMCs were separated from blood samples on Ficoll-Hypaque and percoll density gradients. Percoll density gradients were used to separate the cells into four fractions. Each fraction was collected and stained using immunofluorescent antibody markers to isolate and quantify ImC as well as mature cell populations. ImCs (Lin-) were stained using Lin-, CD115, and CD15; Mature myeloid cells (Lin+) via CD3, CD16, CD19, CD20, and CD56. Flow-cytometry and total cell numbers aided in the quantification of the cell types present. Blood fraction II from patients with cancers should be found to contain higher quantities of ImCs. This experiment is the first step in identification and isolation of this ImC population from cancer patients. Such characterization will be crucial for the identification and the treatment strategies on ImCs, which may induce immune tolerance in human cancer patients.

Risk of Myocardial Infarction or Vascular Death after First Ischemic Stroke: The Northern Manhattan Stroke Study. M.S. Dhamoon, BA[1], R.R. Sciacca, EngScD[2], B. Boden-Albala, DrPH[3,4], T. Rundek, MD, PhD[4], R.L. Sacco, MD, MS[4,5,6], and M.S.V. Elkind, MD, MS[4,5]. [1]Joseph P. Mailman School of Public Health, [2]Department of Medicine, College of Physicians and Surgeons, [3]Department of Sociomedical Sciences, Joseph P. Mailman School of Public Health, [4]Department of Neurology, College of Physicians and Surgeons, [5]Sergievsky Center, College of Physicians and Surgeons, and [6]Division of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

In national guidelines, absolute long-term risk of myocardial infarction (MI) or vascular death determines target low-density lipoprotein (LDL) levels, but stroke patients are not explicitly addressed. We sought to determine 5-year rates and predictors of cardiovascular outcomes after first ischemic stroke in a multiethnic cohort.

Methods: In the population-based Northern Manhattan Stroke Study, first ischemic stroke patients >40 years were prospectively followed annually for recurrent stroke, MI and cause-specific mortality. Kaplan-Meier 5-year rates for cardiovascular events were calculated. Multivariate Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (HR, 95% CI) for predictors of individual and combined cardiovascular outcomes.

Results: Mean age (n=655) was 69.7 ± 12.7 years; 55.4% were women, 51.3% Hispanic. Median follow-up for survivors was 4.0 years. The 5-year rate of MI or vascular death was 16.5% (95% CI 13.4 – 19.6%). Predictors of MI or vascular death were age >70 years (HR 1.86, 1.16 – 2.98), history of MI (HR 1.90, 1.19 – 3.05), and history of atrial fibrillation (HR 2.11, 1.24 – 3.59). Even for the lowest risk group, those <70 years without coronary artery disease (CAD), 5-year rates of MI or vascular death were 9.5% (95% CI 5.5 – 13.4%). Including nonfatal stroke as an outcome measure, the 5-year risk of cardiovascular events was 25.2%.

Conclusion: The absolute rate of MI or vascular death after ischemic stroke is high enough, even without concurrent CAD, to warrant inclusion of ischemic stroke patients in the category of coronary risk equivalents, implying target LDL levels <100 mg/dL for ischemic stroke patients.

The Impact of the Attitudes and Stigmas of Children Regarding HIV/AIDS on Preventing the Spread of Infection in the Bronx, New York. N.E. Edmondson, and M. McKay Ph.D. Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

In the light of the high rates of HIV infection in the Bronx, New York, this study examines the attitudes, stigmas, and knowledge of children regarding HIV/AIDS before they reach high risk age groups. The study aims to determine the origins of these views as well as how this information can be used by physicians to better educate their young patients. Despite recent research advances, HIV/AIDS remains a highly stigmatized disease in the United States. There are many published theories about HIV prevention, but there is a lack of information about children, who are already developing ideas and beliefs that will influence future health decisions. By focusing on understanding these attitudes and stigmas of children regarding the disease, this study aims to discover more effective HIV/AIDS prevention techniques specifically for children. Data for this study will be collected by interviewing and surveying children ages nine to thirteen in the Bronx to examine their beliefs and knowledge of several aspects of the disease. The study began by interviewing children whose parents help organize HIV prevention programs in their community. Next, these children of knowledgeable and motivated parents will be compared to children whose parents are not involved with AIDS prevention programs. The conclusions of these studies could shed light on how the attitudes of children impact the spread of HIV/AIDS, the role of the family in AIDS prevention, and new education and prevention techniques for physicians.

The Stark Study: A Cross-Sectional Study of Adherence to Short-Term Drug Regimens in Urban Kenya. A.E. Ellis, R.P. Gogel, B.R. Roman, J.B. Watson, D. Indyk, PhD, and G. Rosenberg, PhD. Department of Community and Preventative Medicine, Mount Sinai School of Medicine, New York, NY.

The purpose of the STARK study (Short-Term Adherence Research in Kenya) was to identify factors that predict adherence to short-term drug regimens in Nairobi, Kenya. Despite the deleterious effects of nonadherence on patients, limited literature exists on adherence to short-term regimens. The 357 participants enrolled in the study were predominantly mothers under the age of 30 living in nuclear families with an average of three children. Sixty percent of the participants had attended upper primary school. The average weekly income was $2.50, while average weekly expenses were triple that amount. The participants were recruited from the RAFIKI Foundation Clinic, a free primary healthcare clinic in Kibera, Nairobi's largest slum. Quantitative surveys were administered in Swahili to 357 participants regarding their adherence patterns; surveys were also given to a subgroup of 233 mothers regarding their adherence in giving medicine to their children. Forty participated in four focus groups. The study population strongly believed that Western medicine was instrumental in making them well. Fifty-two percent of participants reported taking all of their prescribed medication and 47% took it until they felt better. The most frequently cited barriers to adherence included lack of food and clean water, stress, financial problems, and cost of medication. For the mother-child subgroup, over 65% of mothers reported giving all prescribed medication to their children and cited lack of food as the key barrier to adherence. The amount of control that participants felt they had over their health was positively correlated with how they described their overall health status, and participants reported that greater financial stability would help them to feel greater control over their health. The free nutritional feeding program and caring doctors and nurses made it easier for them to take their medications on schedule. By identifying obstacles to adherence and strategies to overcome them, this study showed that a community-based clinic with committed healthcare workers in Kenya can empower an economically disadvantaged population to be adherent.

Inducible Sirna Targeting of Tumor Suppressor KLF6 Splice Variants and the Effects on in vivo Tumorigenicity. F. Feller, O. Camacho-Vanegas, and J.A. Martignetti. Department of Human Genetics, The Mount Sinai School of Medicine, New York, NY.

The Kruppel-like factor six (KLF6) gene is a tumor suppressor and its functional inactivation is increasingly becoming implicated in a variety of cancers, including prostate, ovarian, and head and neck squamous cell carcinoma. Most recently, we have demonstrated in a multi-institutional study of 3,411 men, that a germline KLF6 single nucleotide polymorphism (SNP) is significantly associated with increased prostate cancer risk. This SNP results in the increased transcription of two alternatively spliced KLF6 isoforms. These splice variant proteins are mislocalized to the cytoplasm and antagonize wtKLF6 function, leading to decreased p21 expression and increased cell growth. To directly examine the in vivo biology of these KLF6 variants we have generated inducible cell lines which specifically silence each of the KLF6 family members. Using this system, the biological effects of KLF6 and its variants can be demonstrated in a temporally restricted manner on a variety of levels from cell culture to in vivo tumorigenesis. With these cell lines, we will explore the effects of independent and targeted siRNA mediated reduction of both KLF6 splice variants on cell proliferation, colony formation, invasion, and in vivo tumorgenicity. Ultimately, these results may provide insight into the molecular mechanisms which underlie the development and/or progression of cancer.

In-vitro Generation of Pancreatic Beta Cells from Embryonic Stem Cells Using Transcription Factors. E. Galeano and T. Ku. Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, NY.

Insulin Dependent Diabetes Mellitus (IDDM), also known as Type 1 diabetes, is a chronic disease in America. The disease is caused by the loss of beta cells in the pancreas, which are responsible for the production of insulin. The disease is treated with daily insulin intake. Injected insulin, however, cannot accurately mimic the natural insulin response, and there are still serious long-term health risks associated this treatment. Replacing the lost beta cells would perhaps be an effective cure; one possible source of beta cells would be embryonic stem cells (ES cells). Past research has been able to differentiate ES cells into early pancreatic insulin and glucagon expressing cells (Ku et al., Stem Cells, in press). Pax 4 is a transcriptional repressor that functions by repressing the alpha cell differentiation program and thus allows the cells to develop into beta and delta cells. This research project will focus on overexpressing Pax 4 using a doxycycline inducible system and monitoring the effects of upregulating the genes in ES derived cells. Doxycycline treated cells will be assayed for insulin and glucagon expression after one to four weeks. This will be the first step toward differentiating cells that secrete insulin. Mature pancreatic cells can be used as a treatment for Type 1 diabetes.

The Relationship between Palliative Care and Hospital Costs. M. Gomez-Trochez, E. Granieri, R.S. Morrison, and J.D. Penrod. Department of Geriatrics, Mount Sinai of Medicine, New York, NY.

Palliative care has been developed to improve care at end of life and for advanced illness. Other studies have examined the effectiveness of palliative care, the most pronounced effect being an improvement of patient and family satisfaction. Despite the prevalence of palliative care in our hospitals, there are few empirical studies comparing the costs of palliative care and usual care. We conducted a retrospective analysis of all the patients who died in the Brooklyn VA hospital, of non-traumatic causes, during fiscal year 2003 We identified patients who did and did not receive a Palliative Care Consultation Team (PCCT) consult during their terminal stay, and matched patients in the two groups based on principal diagnosis, age and co-morbidity. Forty-three PCCT patients were matched to 43 usual care patients. We looked at differences in direct, pharmacy and ancillary cost (average cost per day). There was no significant difference between groups in terms of age, co-morbidity score, number of hospital stays in the previous year or length of stay. PCCT patients had an average 15% fewer days spent in the ICU over the total hospital stay, to a significant degree We also found significantly lower PCCT costs in average direct and average ancillary costs, and no significant difference in pharmacy costs We conclude that palliative care incurs lower hospitalization costs at end of life than does usual care, while providing an array of services that may improve care

The Association between History of Depression and Angiographic Extent of Coronary Artery Disease. J.S. Goodman, N. Rieckmann, D. Haas, D. Shimbo, and K.W. Davidson. Integrative and Behavioral Cardiology, Mount Sinai School of Medicine, New York, NY.

Background: Coronary artery disease (CAD) patients with a history of depression are at increased risk for mortality. It is unclear what mediates this relationship. We examined the relationship between self-reported history of depression and the extent of cardiac disease as indicated by angiography. We hypothesized that patients with a positive history of depression would exhibit greater extent of CAD when compared to patients with no history.

Methods: Participants included 93 post-Acute Coronary Syndrome (ACS) patients. History of depression was assessed using the Depression Interview Scale (DIS). Measures of disease extent were obtained from angiography.

Results: There was no association between depression history and presence of left main or 3 vessel disease and maximum percent stenosis ($p>0.20$). However, number of diseased coronary vessels was significantly lower in patients with a depression history ($p=0.05$).

Conclusions: Contrary to our expectations, patients with depression history did not exhibit greater angiographic extent of CAD and even had fewer significantly diseased vessels. Several previous studies have shown that various severity markers of CAD are not associated with current depression. We review those studies that have examined the relationship between depression and CAD severity markers. Furthermore, we discuss the implication these results have on the pathophysiologic theories underlying higher rates of mortality in depressed CAD patients.

Restorative Proctocolectomy and Ileal Pouch Anal Anastomosis in a Patient with Ulcerative Colitis and Primary Sclerosing Cholangitis following Liver Transplant. A. Grucela and R. Steinhagen, M.D. Division of Colorectal Surgery, Mount Sinai Medical Center, New York, NY.

Primary sclerosing cholangitis (PSC) is present in 5% of patients with ulcerative colitis (UC). Conversely, as many as 90% of patients with PSC have been found to have UC. The accepted treatment for advanced PSC is orthotopic liver transplant, and the treatment of ulcerative colitis with concomitant PSC is restorative proctocolectomy with ileal pouch anal anastomosis (IPAA). A small number of studies have shown that there is an increased risk of pouchitis in UC patients with PSC following ileal pouch anal-anastomosis. We reviewed the literature of restorative proctocolectomy with IPAA in patients with previous liver transplant for PSC and, additionally, reported a case of a 45-year-old male who underwent a two-stage restorative proctocolectomy with IPAA after previous orthotopic liver transplant for PSC. The goal of this investigation was to see if additional factors such as orthotopic liver transplant for PSC, and immunosuppression prior to IPAA, effect the outcome of the surgery. Our primary area of concern was pouchitis, and whether these results require a change of patient management. We concluded that no change in management is warranted for intractable UC in patients who have had previous orthotopic liver transplants for PSC. However, it is important to be aware of the possibility of increased pouchitis risk postoperatively, and to follow these patients closely to avoid complications. The data is speculative, as patient populations are small, and there is a need for further study in this area.

Local Anesthetics and Labor Epidural Analgesia: Bupivacaine vs. Ropivacaine vs. Levobupivacaine. N.R. Guinn, BS, and Y. Beilin, MD. Department of Anesthesiology and OB/GYN, Mount Sinai School of Medicine, New York, NY.

For many years, the local anesthetic bupivacaine has been the standard anesthetic for labor epidurals because of its analgesic effectiveness, differential sensory-to-motor blockade, and its relative long-lasting effects. The FDA has approved two new drugs, ropivacaine and levobupivacaine, which may be safer, having less cardiotoxicity as well as less lower extremity motor blockade. This in turn may correlate with a lower rate of cesarean and forceps assisted delivery. Vaginal deliveries are safer and more cost effective than instrumental deliveries. Thus an anesthetic that decreases the rate of instrumental deliveries while still providing sufficient analgesia would be preferable. This study is looking at the difference in the rate of instrumental deliveries between the three local anesthetics. In a randomized, double blind study, women in labor were assigned to receive one of these three drugs in their epidural catheter. They were assessed for pain, blood pressure, nausea, pruritus, and motor blockade of lower extremities throughout labor, and mode of delivery. Preliminary results show that bupivacaine has the highest cesarean (35%) and total instrumental delivery rate (40%). Levobupivacaine shows lower rates of instrumental (32.4%) and cesarean (26.5%) delivery but with a higher average dose of local anesthetic than the other anesthetics. Ropivacaine has a similar cesarean (25.6%) delivery rate to levobupivacaine but larger instrumental delivery rate (38.4%). Thus far, levobupivacaine appears to be the best local anesthetic for labor epidurals, given the significantly lower rate of cesarean and instrumental delivery rate. We plan on enrolling a total of 360 patients.

Healthy Food Availability in Guadalajara, Mexico, Compared to New York City. M.M. Haglund and C.R. Horowitz, MD, MPH. Department of Health Policy, Mount Sinai School of Medicine, and the East Harlem Diabetes Center of Excellence, New York, NY.

Eating a healthy diet is essential for preventing and controlling diabetes and obesity, which disproportionately affect Mexicans and Mexican Americans. In minority communities in the US, there is a relative shortage of stores that carry nutritious foods. Stores in East Harlem, New York City, an urban, predominantly poor and minority community, are significantly less likely than stores in the predominantly wealthy and white Upper East Side to carry healthy foods. It is not known whether this disparity in healthy food availability exists in developing countries, where many urban US immigrants originate. Therefore, I studied food availability in Mexico, and compared it to food availability in NYC. I surveyed the grocery stores in wealthy and poor neighborhoods of Guadalajara, Mexico, to determine whether they carry healthy versions of five staple foods: fresh fruits, fresh vegetables, high fiber or low carbohydrate breads, low fat milk, and diet sodas. Overall, 11% of stores in the poor, versus 72% in the wealthy area, carry all 5 healthy items, as compared with 18% in East Harlem and 58% on the Upper East Side. In conclusion, there is an even greater disparity between healthy food availability in affluent and low income communities in Guadalajara than there is in NYC. Given that obesity and diabetes are epidemic in both nations, efforts should be made to determine the effect of this disparity on diet and on health, and to improve availability of healthy foods. Efforts to educate US immigrants on healthy eating should recognize that individuals may be from environments where they had limited exposure to healthy foods.

Prevalence and Characteristics of Physician-Older Adult Communication about Complementary Alternative Medicine Use in East Harlem, New York. S.Y. Hu, C.X. Pan, and J.L. Howe. Departments of Geriatrics and Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Previous research shows that CAM is widely used among older adults, often without knowledge by their physicians (Cohen RJ, Pan CX, 2002). This pilot study is a follow-up to find the possible causes of the physician-older adult communication barrier regarding the use of CAM in an urban low-income community. We compared the demographics and the types of CAM used by the communicators and the non-communicators to assess predictors of lack of discussion about CAM use between physicians and patients. Of the communicators, we also assessed physician characteristics that facilitate discussion as well as the elders' perceived usefulness of these discussions. One hundred surveys administered in Mandarin, Spanish and English were acquired from interviewing elders living in government subsidized housing facilities, i.e., Linkage House, and participants of the East Harlem senior centers Gaylord White, James Weldon Johnson, Corsi and Washington/Lexington. Preliminary results agree with our hypothesis that older adults in East Harlem tend not to talk to their doctors about CAM use, as supported by a communication rate of about 33% among CAM users. Hispanics and Asians are more likely not to talk to their physicians, with Asians being the most unlikely. Analysis on other predictors of communication barriers about CAM, such as doctor-patient language concordance and type of CAM usage, is ongoing. With the results of this study, we hope to assess the predictors of poor physician-older adult communication on CAM use, which may serve as a basis for future public health initiatives and physician education.

Trauma Exposure and PTSD in an Inner-City Outpatient Clinic. A. Hurtado, J. Newcorn, E. Greenblatt, T. Brennan, D. Charatan, I. Ivanov, E. Shemesh, C. Chemtob, R. Yehuda, A. Garnacho, and C. Hamilton. Department of Adolescent Child Psychiatry, Mount Sinai School of Medicine, New York, NY.

Childhood exposure to traumatic stress has been widely recognized as a prominent risk factor in the development of psychopathology in childhood and later life. This is of particular importance in urban areas, where children have been found to be repeatedly exposed to traumatic events. Nevertheless, much of the literature disproportionately discusses youth exposed to single event traumas, such as natural disasters. Therefore, the relationship between traumatic experiences encountered by children living in high-risk environments and childhood psychiatric disorders remains poorly understood. In order to examine the prevalence of traumatic exposure and PTSD symptoms, 203 children visiting Mount Sinai Hospital's outpatient child psychiatric clinic for the first time were recruited. Participating children were between the ages of 4 and 17. Parent and child were asked to complete a series of psychiatric measures that include the UCLA Post-traumatic Stress Reaction Index. We found that 68% of these children reported some type of trauma. The most common trauma reported was related to domestic violence. Based on child reports, 44% of the children meet either full or partial PTSD criteria. The parent reports, however, demonstrate that 31% meet full or partial criteria for PTSD. Furthermore, 68% of children reported any trauma, while only 59% of parents reported any trauma. Of the 31 children who met full PTSD diagnosis, based on parent report on PTSRI, only 7 were diagnosed with PTSD by clinicians. Similarly, 7 of the 30 children meeting full criteria based on child PTSRI reporting were diagnosed with PTSD. This data suggests that traumatic stress may be under-appreciated by parents and underdiagnosed by clinicians.

Induction of Apoptosis by HIV-Infected Monocytic Cells. F.S. Hwang and K. Sperber. Department of Medicine, Center for Immunobiology, Mount Sinai School of Medicine, New York, NY.

We have cloned an apoptotic protein, the human hypothetical protein FLJ21908 isolated from the CD14lowCD16high 43 HIV human macrophage hybridoma cell line that we have renamed the SHIVA (soluble HIV apoptotic) protein. SHIVA may play a role in the neurological complications of AIDS, especially HIV-associated dementia (HAD), since it induces apoptosis in neuronal cells, can be co-localized in brain macrophages of patients with HAD by immunohistochemistry, and is detected (ELISA and PCR) in the cerebrospinal fluid of patients with HAD but not in HIV-infected patients without dementia, or normal controls. We have identified 2 candidate receptor(s) (MW 100 kDa) for SHIVA and demonstrated that SHIVA-induced apoptosis can be blocked by memantine (an NMDAR antagonist), anti-oxidants and transfected Bcl-2 in neuronal cell lines. SHIVA causes apoptosis by activating Bad and Bax, suppressing Bcl and Bcl-xL, and releasing cytochrome c from the mitochondria that activates caspase 9 and caspase 3. We analyzed brain tissues of patients with HIV-1 Associated Dementia (HAD) obtained from the Manhattan AIDS Brain Bank, located here at The Mount Sinai Medical Center. We have determined the presence of SHIVA and other apoptotic factors, including TNF-alpha, gp120 and Tat in the frontal lobes, basal ganglia and the sub-cortical white matter in HIV patients with HAD, compared to HIV patients without HAD and normal controls with immunohistochemistry. We will analyze those stains showing apoptosis via morphometric analysis to further characterize the role of SHIVA.

Assessment and Review of HIV-Positive Patient Medical Records from a Traditional Siddha Medicine Hospital in Tamil Nadu, India. S. Ikeda, K. Baban, N. Hennig, MD, PhD, and H. Sacks MD, PhD, Thomas C. Chalmers Clinical Trials Unit, Mount Sinai School of Medicine, New York, NY.

Only a small percentage of people worldwide have access to HIV antiretroviral therapy and many rely on indigenous medicine systems. For this reason, WHO through the World Health Assembly in 2002 identified the study of these methods as a priority. Siddha medicine, one such traditional system, originated in Tamil Nadu, an impoverished state in south India bearing a disproportionate percentage of the country's HIV/AIDS cases. As part of a long-term goal to evaluate the efficacy of Siddha medicine as a therapy for HIV, we assessed the medical record-keeping system of Gandeepam, a Siddha hospital in rural Tamil Nadu. Because traditional medicine systems do not necessarily keep records of their patients, it cannot be assumed that such records exist nor that they resemble Western patient charts. However, Gandeepam had begun keeping records two years prior. The records of 36 HIV positive patients were randomly selected from a total of 87 cases. Diagnoses, adherence to treatment, changes in patient health status, adverse events, and a system of unique patient identifiers employed by Gandeepam for a previous study were documented and evaluated. Preliminary findings indicate the records included patient symptoms, treatments prescribed, and changes in patient status. However, little insight into Siddha diagnoses or adverse reactions were provided. Additionally, patients' identifying information was linked to their unique study number within the chart. Recommendations for improvement to Gandeepam's medical record system based on these findings will pave the way for continued collaboration with Gandeepam, and future clinical studies of Siddha medicine.

Regulation of CA2+-Regulating Enzymes, CD38 and CD157, by TNF-A during Osteoclastogenesis. J. Iqbal and M. Zaidi. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

CD38 and CD157 are evolutionary conserved ecto-enzymes that catalyze the conversion of NAD+ to Ca2+-releasing molecules. The expression of both CD38 and CD157 is enhanced in severe rheumatoid arthritis, the osteolysis associated with which is TNF-mediated. We therefore examined whether CD38 and CD157 were positively regulated by TNF as a means to control excessive osteoclastogenesis. TNF-a stimulated, by >30- and >8-fold respectively, the expression of CD38 and CD157 mRNA in ficoll-purified bone marrow cells for up to 48 hrs. This was expectedly not seen with CD38- - cells, confirming specificity. Double-labeling experiments showed that both CD38 and CD157 were up-regulated in the same cells. To understand the mechanism of the TNF-a effect, we carried out half-life experiments, ChIP and DNA binding assays. Both CD38 and CD157 mRNAs in TNF-a treated cells displayed half-lives of about 3 hrs, excluding effects on mRNA stabilization. Consistent with this, we detected binding of an NF-kB responsive element in the murine CD38 promoter to the NF-kB subunit, p50. This binding was abrogated when a G->C point mutation was introduced within promoter, confirming specificity. ChIP analysis showed increases in p65/p50/c-fos binding to the CD38 promoter 3 hours after TNF addition. In contrast, RANK-L treatment failed to increase NF-kB binding to the promoter. Re-ChIP analysis at 3 hours after TNF addition showed that p65/p50/AP-1/STAT1 all bound to the CD38 promoter and were able to immunoprecipitate each other. As CD38 negatively regulates osteoclast formation, its up-modulation may provide a primary mechanism for controlling the TNF-a-driven osteoclastogenesis in rheumatoid arthritis.

The Epidemiology of Molecular Markers and Breast Cancer Prognosis. W.R. Jimenez and J. Bernstein. Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Many studies have examined the relationship between survival and molecular markers. However, there are only a few studies on the association between epidemiologic risk factors for breast cancer, molecular markers (p53, Her-2/neu, estrogen receptors and progesterone receptors) and prognosis. The Cancer and Steroid Hormone Study (CASH) provides a unique opportunity to study the association between epidemiologic risk factors, molecular markers, and prognosis because of: (a) the large number of women enrolled: and (b) the availability of extensive interview information, and annual follow-up data. All 4,660 CASH patients were between 20 – 54 years of age with a diagnosis of a first primary breast cancer between 1980 – 1982 ascertained through 5 population-based SEER tumor registries, and interviewed within 6 months of their initial diagnosis. For the current analyses, tumor tissue is available for 1200 cases. Using the combined CASH interview data and SEER follow-up data, we are conducting an association study of the epidemiologic risk factors and molecular markers. In addition, we will also study whether there are variations in survival in subgroups in which epidemiologic risk factors for breast cancer are associated molecular markers. Our work focused on identifying important risk factors associated with the molecular markers by reviewing the literature. The identified risk factors will be used to guide variable selection in the analysis and interpretation of the results. The results of this study may help identify more homogenous subgroups of women with breast cancer, and consequently better-tailored treatment options.

Evaluation of Dynamic Contrast Enhanced Perfusion MRI in Kidney Disease. P.E.M. Johnson and J.P. Goldman. Department of Radiology, Mount Sinai School of Medicine, New York, NY.

Chronic Renal Insufficiency (CRI) is a largely asymptomatic epidemic thought to affect more than 10 million Americans. If left unchecked, CRI progresses to End Stage Renal Disease (ESRD), the incidence of which is rapidly increasing, and represents a significant, growing and largely preventable health care burden. The key to prevention lies in arresting CRI before it progresses to ESRD, an intervention that rests heavily on diagnosis. We have developed a new dynamic contrast enhanced perfusion MRI (DCE-MRI) for the quantitative measurement of kidney perfusion. The procedure is both rapid and minimally invasive. It is our hypothesis that quantitative MRI measurements of kidney perfusion will provide useful information in assessment of kidney pathology. We applied this technique in scans of 12 normal controls and of 4 patients with a diagnosis of CRI. Additionally, 8 of the 12 controls had a second scan several weeks after the initial scan. Scans were analyzed to produce descriptive data related to the blood flow into and out of the region of interest. We found no significant difference in measures between the two sessions for those control subjects that had repeat scans. Significant differences were found between control and patient groups in measures of both cortical and medullary diffusion ($p<0.01$), and in cortical perfusion rates ($p<0.001$). While we must be conservative with a small sample size, initial findings suggest that DCE-MRI may provide a new technique for the diagnosis and assessment of CRI and related kidney pathology.

Evaluation of the Individual Herbs of FAHF-2 in a Murine Model of Peanut Allergy. J.D. Kattan and X-M Li. Division of Pediatric Allergy and Immunology, Mount Sinai School of Medicine, New York, NY.

Peanut allergy is a major cause of fatal and near-fatal anaphylactic reactions. It has no curative therapy. Our lab has shown that a Chinese herbal formula, Food Allergy Herbal Formula 2 (FAHF-2), blocks peanut-induced anaphylaxis in a murine model. This study was designed to investigate the effects of the nine herbs in FAHF-2, to see their individual effects on peanut-induced anaphylactic reactions in a mouse model of peanut allergy. Mice were sensitized with freshly ground whole peanut in the presence of cholera toxin. After herbal treatment for 7 weeks, mice were challenged with peanut, and anaphylactic symptoms, body temperatures, and plasma histamine and IgE levels were measured. T-cell proliferative responses and cytokine production were also determined. In our trials, some single herbs lessened peanut-induced anaphylactic symptoms, though no herb offered full protection from anaphylactic symptoms. The herbs had highly variable effects on mast cell degranulation and histamine release, as well as peanut-specific serum IgE levels. The herbs also had different effects on cytokine production. In conclusion, individual herbs offered varying amounts of protection from anaphylactic reactions, while no single herb supplied complete protection. This suggests that the herbs of FAHF-2 work synergistically to produce the curative therapeutic effects seen in the overall formula, and that each of these herbs may be necessary in future trials of FAHF-2. Further studies must be done to see if all nine herbs are necessary to prevent an anaphylactic reaction in a mouse model of peanut allergy and, ultimately, in a human model.

Rihavirin Suppresses eIF4E-Mediated Oncogenic Transformation by Physical Mimicry of 7-Methyl Guanosine mRNA Cap. A. Kentsis, I. Topisirovic, B. Culjkovic, L. Shao, and K. Borden. Structural Biology Program, Department of Physiology and Biophysics, Mount Sinai School of Medicine, New York, NY.

The eukaryotic translation initiation factor eIF4E is deregulated in many human cancers, and its overexpression in cells consistently leads to malignant transformation. Oncogenic properties of eIF4E are directly linked to its ability to bind 7-methyl guanosine of 5' mRNA. Here, we observe that antiviral guanosine analogue ribavirin physically mimics 7-methyl guanosine under physiological conditions. As a result, ribavirin binds to eIF4E with uM affinity at the functional site used by 7-methyl guanosine mRNA cap, competes with eIF4E:mRNA binding, and at low uM concentrations selectively disrupts eIF4E subcellular organization and transport and translation of mRNAs post-transcriptionally regulated by eIF4E, thereby reducing levels of oncogenes such as cyclin D1. Ribavirin potently suppresses eIF4E mediated oncogenic transformation of murine cells in vitro, tumor growth of a mouse model of eIF4E dependent human squamous cell carcinoma in vivo, and colony formation of eIF4E dependent acute myelogenous leukemia cells derived from human patients. These findings describe a specific, potent, and unforeseen mechanism of action of ribavirin. Quantum mechanical and NMR structural studies offer directions for the development of derivatives with improved cytostatic and antiviral properties. In all, physical mimicry of 7-methyl guanosine by ribavirin may provide a pharmacologic means for the interruption of post-transcriptional networks of oncogenes that maintain and enhance neoplasia and malignancy in human cancer.

From Frizzled to Dishevelled: Molecular Mechanisms of Signal Specificity. T.J. Klein and M. Mlodzik. Brookdale Department of Molecular, Cellular and Developmental Biology, Mount Sinai School of Medicine, New York, NY.

Canonical Wnt/Fz signaling is important for the regulation of a vast array of developmental processes and, when mutated, is associated with a number of human diseases, including lung, breast, colon, and prostate cancer. Two members of the canonical Wnt/Fz pathway, the transmembrane receptor Frizzled (Fz) and the cytoplasmic factor Dishevelled (Dsh), are not only important for canonical Wnt/Fz signaling, but also regulate a distinct non-canonical pathway that controls planar cell polarity (PCP). PCP signaling regulates processes in which cells are polarized relative to one another within the plane of a tissue. We are interested in understanding how Fz and Dsh specifically transduce signals to one pathway versus the other. To do this, we generated a series of canonical/non-canonical chimeric Fz receptors designed to answer this question. We expressed these receptors in both the *Drosophila* eye and wing, and scored for canonical and non-canonical phenotypes. Using this method, we identified key regions of Fz required for signaling specificity. We also established assays in cell culture and the *Drosophila* wing to study the recruitment of Dsh by both canonical and non-canonical Fzs. Experimental results using these assays demonstrate a requirement for heterotrimeric G-protein signaling specifically for the recruitment of Dsh by non-canonical Fzs. To confirm these results, we analyzed genetic interactions between Fz, Dsh, and G-protein signaling effectors and found a requirement for PLCβ in transducing non-canonical signals.

Availability of Physical Activity Resources for Children in the Urban Environment of East Harlem. J.H. Kobil and M. Galvez. Departments of Community and Preventive Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY.

Childhood overweight and obesity have become epidemic in the United States, especially among African-American and Latino children. East Harlem, a predominantly minority community, has the highest prevalence of obesity of any neighborhood in New York City. Physical inactivity is a major risk factor for obesity. The community-based participatory research project, "Growing Up Healthy in East Harlem," is exploring the relationship between children's growth and development and the physical or "built" environment. A comprehensive survey of East Harlem zip codes 10029 and 10035 was performed through (a) direct observation via walking tours of the neighborhoods and (b) compiling information from various local and state internet sources and city/state agencies. A series of maps of physical activity resources available to East Harlem children has been developed using the geographic information systems software package, ArcGIS. These maps provide location information on resources such as public parks, playgrounds, pools, recreation centers, after-school activities, dance lessons, and sports instruction and teams. Preliminary analysis of the maps will provide information on distribution of resources throughout the community. The maps will be used to examine the effect of access and utilization of physical activity resources on levels of overweight and obesity in East Harlem children. Additionally, the maps will be distributed to East Harlem residents by pediatricians, community health organizations, and the New York City Department of Health's district public health office in East Harlem. The maps will thus serve as a community resource for physical activity opportunities available to children in East Harlem.

Ex vivo Magnetic Resonance Microimaging of the Tg2576 Transgenic Mouse Model of Alzheimer's Disease: Determining Volumetric Changes in the Brain. M.H. Kujawski[1], C.Y. Tang[2,3], and Patrick R. Hof[1,3]. Departments of [1]Neuroscience, [2]Radiology, and [3]The Advanced Imaging Program, Mount Sinai School of Medicine, New York, NY.

The pathogenesis of Alzheimer's disease (AD) is characterized by the deposition of neurofibrillary tangles and amyloid plaques in brain regions associated with memory and cognition. Abnormal amyloid metabolism and its subsequent deposition as plaques in the brain can lead to neuronal damage and synapse dysfunction. This project addresses the relationship between plaque deposition and cerebral attrition in the Tg2576 mouse model of AD. It is hypothesized that there is an age-dependent volume loss in regions of the Tg2576 mouse brains that are specifically vulnerable in Alzheimer's disease, such as the hippocampus and entorhinal cortex. The Tg2576 model expresses the "Swedish" double mutation of the amyloid precursor protein, exhibiting diffuse deposition of beta-amyloid plaques in areas of the brain vulnerable in AD. Ex vivo magnetic resonance microimaging (MRM) is performed at 9.4 Tesla to generate a high-resolution, three-dimensional image. The image is imported into Amira software for segmentation of brain regions in three orthogonal planes to obtain volumetric measures of the specified regions. Regions of interest include areas afflicted by plaque deposition in AD, such as the hippocampus, the entorhinal cortex and the neocortex. This project therefore examines the temporal and spatial progression of neuronal pathology in a quantitative manner. Preliminary data yield regional volumes that are consistent with values obtained from histological specimens. We plan to expand this project to in vivo MRM, which will allow us to follow pathologic changes prospectively within the same animal during aging, as well as assess the effect of preventive measures on disease progression.

The Role of Atherosclerotic Risk Factors in Aortic Remodeling: a Comparison of New York Latinos to Native Mexicans. A.A. Lambert and M.E. Goldman. Cardiovascular Institute and The Center for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY.

Aortic dilatation is a progressive disease which can lead to aneurysm and rupture. Atherosclerotic risk factors (smoking, diabetes, age, and hypertension) are associated with thoracic and abdominal aortic dilatation. Medically underserved populations have more risk factors leading to progressive aortic dilatation as compared to better served populations. To test whether thoracic aortic abnormalities correlate with quality of medical care, two populations were evaluated—the general population served by Mount Sinai Hospital, which includes an underserved population, and the native Mexican population of Guadalajara, Mexico. This study had three aims: (a) to correlate aortic dilatation with classic atherosclerotic risk factors; (b) to examine the rate of progression of dilation in successive echocardiograms; and (c) to compare aortic size and risk factors for the Latinos living in East Harlem to those living in Guadalajara, Mexico, as well as to the non-Latino population. Thus, once patients consented to participate in an IRB-approved study, a detailed interview was conducted to assess their risk factors prior to their 2D echocardiogram, which specifically measured thoracic aortic diameter. Presently, the patient population consists of 127 patients recruited from New York City and 32 from Guadalajara, Mexico. Analysis is currently being conducted. Results of this study may provide insight into whether genetic or environmental variables play an important role in aortic remodeling.

Violence Intervention and Prevention Education Program. D. Laochamroonvorapongse, M. Foley, EdD, E. Garland, MD. Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Domestic violence is a major public health problem, affecting as many as one in five families in this country. Despite this staggering figure, primary care providers often fail to screen for domestic abuse or recognize the warning signs that may suggest the potential for escalation of violence. To date, violence screening practices that do occur have focused almost exclusively on women. A brief screening tool for men, useful in primary care practice, is currently not available. For this study, 18 primary care physicians were interviewed to determine what they currently do to screen for, identify, and refer men who might present in the clinical care setting with intimate partner violence (IPV) tendencies. The collected data shows that all physicians interviewed screen less than 5% of their male patients for IPV, and that they decide to screen only when the patient exhibits aggressive behavior or signs of physical injury. If patients have risk factors for IPV or have committed IPV, most physicians will counsel them on anger management skills and refer them to a social worker or psychiatrist. Drawing from the survey results, we plan to design and pilot test a screening tool in the clinical setting. Then, we will develop a teaching, patient screening, and evaluation module on IPV and family violence and present it as an elective course in the master of public health (MPH) program. This will allow physicians to enhance their ability to conduct early detection and develop preventive response strategies for IPV.

Development of an Animal Model to Assess the in vivo Response of Tendons to Fatigue Loading. H. Lee, V.M. Wang, and E.L. Flatow. The Leni and Peter W. May Department of Orthopaedics, Mount Sinai School of Medicine, New York, NY.

Tendon injuries are among the most common orthopedic pathologies and occur especially frequently in athletes and the elderly. Despite this prevalence, the etiology of tendon rupture is poorly understood, both clinically and scientifically. Based on clinical observations, tendon failure is widely attributed to the process of wear. However, existing studies of tendon healing have incorporated tendon laceration (i.e., wounds) as opposed to direct mechanical loading as the injury model and thus do not model injury progression. In tendons that sustain matrix damage, the extent to which these tissues are capable of matrix-level repair and the biological repair mechanisms are not known. Therefore, we have developed a novel in vivo rodent model to determine how well patellar tendons recover their biomechanical function following experimentally induced fatigue and to elucidate the biologic mechanisms by which tendons respond to matrix-level injury. This approach enables us to determine the relationship between the magnitude (dosage) of tissue mechanical loading and the time course of intrinsic repair. Having developed the techniques and implemented our loading protocols in preliminary fatigue experiments for the patellar tendon, we will initiate our in vivo studies shortly. Our quantitative histological and biomechanical results will provide much needed insight into the nature of damage accumulation in tendons and their biologic repair response. These will constitute the first reported data on intrinsic tendon repair following mechanical loading. Future studies using this model may result in the earlier diagnosis and treatment of tendon injury.

Depression and White Matter Changes in Acute Coronary Syndrome Patients. D.A. Lessman, M. Rapp, C.Y. Tang, R. Paulino, S. Williams, and K. Davidson. Coronary Patients Evaluation Study (COPES). Mount Sinai School of Medicine, New York, NY.

Depression is a common complication in post-acute-coronary syndrome (ACS) patients and has been linked with increased morbidity and mortality when compared to non-depressed ACS patients. However, the neurophysiological correlates of this type of depression are unknown. Studies have demonstrated that frontal white matter changes correlate with depression severity as well as prognosis. It has been proposed that these white matter changes are related to vascular changes and perfusion deficiencies. Furthermore, such relationships have been demonstrated in depressed patients with comorbid diabetes mellitus and hypertension. Because of the implications of depression on the cardiovascular prognosis in ACS patients, it becomes important to ask whether mechanisms that affect vascular integrity and express themselves acutely as unstable angina or myocardial infarction may also be associated with deep frontal white matter changes. To this end, we will be using magnetic resonance imaging (MRI) to measure changes in white matter integrity and cerebral perfusion in ACS patients. We will use a case-control design, comparing depressed and non-depressed ACS patients as classified by the Beck Depression Index (BDI) from the Coronary Patients Evaluation Study (COPES). Previous investigations of this relationship have largely relied on conventional MR methods. Our investigation is primarily using diffusion tensor imaging (DTI), which has been shown to be more sensitive to changes in white matter than other MR methods, and which can also be used to quantify microstructural organization of white matter fibers through fractional anisotropy. We expect to find more extensive white matter changes in depressed patients.

Understanding Influences on Care for HIV/AIDS: the Overlap of Health, Mental Health, and Substance Abuse. E. Levi and M. McKay, PhD, LCSW. Department of Community and Preventive Medicine. Mount Sinai School of Medicine, New York, NY.

Although there are currently medications and health care options that have been shown to greatly increase the quality of life and life expectancy for people living with HIV/AIDS, there are patients who are not accessing or adhering to these health care services and protocols. This study seeks to explore how issues such as mental health difficulties, substance abuse problems, stigma associated with care and disclosure, and competing life priorities may be associated with patients dropping out of or underutilizing outpatient care. Participants in this study will be recruited at an inpatient AIDS unit at Mount Sinai. The participants will be interviewed using standardized instruments, both qualitative and quantitative, regarding a range of topics including: mental health needs, past and present alcohol and substance use and abuse, and barriers to care. The goal of the project is to identify specific barriers to care, so as to inform programs on how to reduce the rate of patient drop-out, make their services more accessible, and ultimately decrease patient mortality.

The Brodmann Areas: Histology and Magnetic Resonance Imaging at 9.4 Tesla. R.J. Lien[1], T.P. Naidich[2], W.G.M. Janssen[3], M.M. Lim[4], and P.R. Hof[3]. [1]Mount Sinai School of Medicine, [2]Departments of Radiology, and [3]Neuroscience Mount Sinai School of Medicine, New York, NY; and [4]University of Scranton, Scranton, PA.

Background: The cytoarchitectonic divisions of the human cortex are traditionally characterized by the histological criteria of Brodmann (1). High-field MRI now displays the intrinsic laminar organization of the human cortex (2). Hypothesis: Correlation of MR images with histological stains of the identical specimens will establish and validate MR criteria for characterizing and identifying the Brodmann areas.

Materials and Methods: Specimens of all numbered Brodmann areas were imaged at 9.4 T to achieve a slice thickness of 500 um and an in-plane resolution of 80 × 80 um, as given in (2). The specimens were cryoprotected with graded concentrations of sucrose and then cryosectioned at serial 50 um intervals. Every 500 um, two adjacent sections were prepared with Nissl (neuron) and Black Gold (myelin) stains, and the stained sections correlated with the corresponding MR images to discern MR criteria for characterizing the Brodmann areas.

Results: MR images displayed the varying thicknesses of the cortex and individual cortical layers, and demonstrated well the presence and relative thicknesses of the bands of Baillarger. Low signal intensity on MR images corresponded to either high cellularity and/or dense myelination.

Conclusion: Changes in MR signal intensities faithfully reflect the cortical histology. MR criteria successfully identify major Brodmann areas, but do not yet distinguish regional subdivisions and boundaries among areas.

1. Brodmann K. Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: Barth; 1909.
2. Fatterpekar GM, Naidich TP, Delman DN, et al. Cytoarchitecture of the human cerebral cortex: MR microscopy of excised specimens at 9.4 Tesla. AJNR 2002; 23:1313–1321.

Drinking Water Guidelines for Operation in Remote Locations. A.L. Ligouri, S.E. Lerman, MD, MPH, and M.D. Hochberg. Mount Sinai School of Medicine, New York, NY; and Exxon Mobil Biomedical Sciences Inc., Annandale, NJ.

Drinking water contamination has been linked to large-scale epidemics, and is still a major cause of mortality due to dysentery around the world. Exxon Mobil, a corporation that operates in a variety of remote locations, must ensure that the employees, contractors and others whom they supply water to are protected from health hazards such as Legionella, coliform bacteria and cholera. Exxon Mobil stands behind its maxim of "Nobody Gets Hurt," and is assisted with ensuring this through their Exxon Mobil Biomedical Sciences Inc. (EMBSI), and Medical and Occupational Health Department (MOH). To this end, they have developed a common process to address expectations for the construction, operation, maintenance and monitoring of potable/drinking water systems, to ensure that potential health risks are identified and controlled commensurate with the risk. To develop this process, a review of the literature including references from the World Health Organization, United States Environmental Protection Agency, American Water Works Association, European Union Drinking Water Directives and Australian Drinking Water Guidelines was conducted. It was concluded that drinking water quality should adhere to World Health Organization Drinking Water Guidelines. The key to making sure that "nobody gets hurt" is that each operating site is to have a Drinking Water Contaminant Control Program in place. Highlights of this contaminant control program are drinking water system configuration, operational/ maintenance expectations, disinfection where chlorine residual is measured, record keeping, operator qualification and training, and emergency situation plan. Exxon Mobil's emphasis on drinking water is a prime example of its commitment to being a responsible global citizen, and should be considered for use as a model for other global corporations.

The Effect of Cataract Extraction and Intraocular Implant on Optic Disc Topographic Measurements. A.A. Macedo, R. Madhok, V.C. Edwards, L.A. Polikoff, and J.B. Serle. Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY.

Background: Glaucomatous optic neuropathy is characterized by progressive loss of ganglion cells. Reliable detection of optic disc changes over time is the mainstay of glaucoma diagnosis, follow-up and treatment. The Heidelberg Retina Tomograph (HRT) was developed as an adjunct to visual field and clinical evaluation of patients.

Purpose: To determine the effects of cataract extraction with intraocular lens placement on HRT parameters in the glaucomatous optic disc.

Methods: Retrospective analysis of 32 patients using HRT and Humphrey Visual Field (HVF) studies from before and after cataract extraction. Pre- and post-op HRTs were compared for changes in the Moorfields Regression Analysis classification globally and in six sectors of the optic disc, as were differences in the 14 variables of the Multivariate Discriminant Analysis. Pre- and post-op HVFs were compared for differences in mean deviation and pattern standard deviation.

Results: Significant increases in the HRT parameter rim volume were detected post-operatively, globally ($p<0.04$), and in the temporal-superior ($p<0.04$) and nasal-inferior sectors ($p=0.023$). Both mean and maximum cup depth were significantly increased in the temporal sector ($p=0.03$, $p=0.036$ respectively). Analysis of the HVFs showed a decrease in mean deviation (1.61, $p=0.002$), but no significant changes in PSD or CPSD.

Conclusion: This study has shown that rim volume and cup depth measurements, which are important in the early detection of optic disc change, are altered by the presence of lens opacity. Based on these findings, a new baseline image should be obtained after cataract surgery in order to properly monitor glaucomatous progression.

Attitudes towards Academic Dishonesty and Professionalism among Medical Students. L.C. Manace, MPh, S. Berns, L.G. Smith, MD, B.D. Stimmel, MD, and S. Rose, MD. Department of Medical Education, Mount Sinai School of Medicine, New York, NY.

Medical education has become increasingly concerned with the ethical integrity and professionalism of physicians in training. Studies examining cheating in medical school have found that a high percentage of students admit to cheating, but more investigation regarding the motivation for dishonest behavior is warranted. This study was designed to evaluate students' self-reported academic dishonesty and their opinions about ethical issues, by an anonymous questionnaire. Across all four years, 13.8% and 15.5% reported that they were academically dishonest once or more often during their pre-clinical and clinical clerkship years, respectively. And 42.9% and 50.5% of students observed academic dishonesty once or more times during their pre-clinical and clinical clerkship years, respectively. Levels of stress were not correlated with cheating. Students who reported they had cheated were more likely to respond that people who are academically dishonest "are not always morally upright." Though 76.6% answered that honor codes would definitely or somewhat reduce academic dishonesty, 54.7% and 86.6% of students replied that a system for documenting professional and unprofessional behavior will not reduce the academic dishonesty of others or themselves, respectively. The results of this study direct the etiology of cheating and unprofessional behavior away from the competitive environment of medical training and towards the individual nature of students. Past reports have shown a comparable or higher rate of self-reported cheating in medical school, but this study is unique in finding that the motivation of students who cheat lies outside the academic pressures of medical school.

Calorie-Restricted Low Carbohydrate Diet Reduces Amyloid Load in Mouse Model of Alzheimer's Disease. K.P. Maniar[1], A. Rocher[1], L. Ho[2], J. Wang[2], G.M. Pasinetti[2], and P.R. Hof[1]. Departments of [1]Neuroscience and [2]Psychiatry, Mount Sinai School of Medicine, New York, NY.

Numerous studies have suggested an association between diet and the aging process. It has been demonstrated that diets with high fat, carbohydrates, or calories may increase the risk of developing Alzheimer's Disease (AD). In this study, the effect of a low-carbohydrate, calorie-restricted diet on a mouse model of AD was investigated. Eleven APP mice, transgenic animals which accumulate amyloid plaques characteristic of AD as they age, were separated into two groups. One was subjected to standard dietary conditions and the other to a 70% calorie restriction, low-carbohydrate diet. The mice were sacrificed and perfused, and brain sections were labeled for the presence of amyloid using thioflavin-S staining. Amyloid load in the prefrontal cortex and hippocampus was estimated by the fractional amyloid load using the Cavalieri principle. The calorie-restricted mice were found to have a significantly lower amyloid load in the prefrontal cortex (52% for standard, 11% for calorie-restricted) as well as in CA1 (50% for standard, 5% for calorie-restricted) and dentate gyrus (33% for standard, 3% for calorie-restricted) of the hippocampus. These results suggest that a low-calorie, low-carbohydrate diet may prevent or slow the progression of AD. By demonstrating a potentially significant environmental contribution to the disease, the results not only have implications for its prevention and treatment, but also provide insight into its causes and etiology. Further studies into other forms of calorie, macromolecule, or nutrient restriction should provide useful results and have promising implications for clinical application to human subjects. Supported by NIH grants AG02219 and AG05138.

Evaluation of the Maternal Immunological Response to the Influenza Virus Vaccine during Pregnancy. N.C. Marcell, A. Fernandez-Sesma[1], C. Gyamfi[2], R.S. Sperling[2], T. Moran[1]. Departments of [1]Microbiology and [2]Obstetrics, Gynecology and Reproductive Science, Mount Sinai School of Medicine, New York, NY.

Traditionally, the lack of rejection of the fetal-allograft led scientists to believe that pregnancy was an immunosuppressed state. Recent evidence shows, however, that the immunological difference between pregnant and non-pregnant women is not merely quantitative, but qualitative. Immune responses can be categorized as either T helper 1 (Th1), typically aimed at viral and bacterial pathogens, or T helper 2 (Th2), seen in parasitic invasion or allergic responses. Th1 responses are proinflammatory and can be so potent that developing fetuses may be attacked, as suggested by high levels of Th1 cytokines in women with recurrent spontaneous abortions. Our goal is to compare immunity in response to the 2003/2004 trivalent, inactivated influenza virus vaccine in pregnant and non-pregnant women. We hypothesized: (a) that pregnant women would have a lower antibody titer than non-pregnant women in response to vaccination and (b) that pregnant women would produce IgG4 antibodies, characteristic of a Th2 response, as opposed to IgG1 antibodies, typical of Th1 responses expected in non-pregnant women. Using hemagglutination inhibition assays to analyze the sera of 33 pregnant and 41 non-pregnant women, before and after vaccination, we found that women in both groups responded with equivalent increases in antibody titer. A/Panama and A/New Caledonia virus strains induced the highest levels of antibody titers; surprisingly, the B/Hong Kong strain elicited very weak antibody responses. We are currently developing an immunofluorescence assay to distinguish between IgG1 and IgG4 antibodies against the influenza HA protein expressed on the surface of transfected cells. This will provide a qualitative assessment of the immune response to vaccination.

The Effect of 6-Mercaptopurine on Progression to Colorectal Neoplasia in Ulcerative Colitis. S. Matula[1], V. Croog[1], S. Itzkowitz[1], N. Harpaz[2], C. Bodian[3], S. Hossain[3], and T. Ullman[1]. [1]The Dr. Henry D. Janowitz Division of Gastroenterology, Department of Medicine; [2]Division of Gastrointestinal Pathology, Department of Pathology; and [3]Department of Biomathematical Sciences, Mount Sinai School of Medicine, New York, NY.

Background: Patients with longstanding, extensive ulcerative colitis (UC) are at increased risk for developing colorectal cancer (CRC). Evidence suggests that mesalamine-based anti-inflammatory medicines may prevent progression to CRC in UC. If mesalamine exerts its chemopreventive effect by reducing mucosal inflammation, then other medications that reduce colitis activity should also possess chemopreventive properties.

Aim: To determine the effect of 6-mercaptopurine (6MP) and azathioprine (AZA) in preventing the development of dysplasia or CRC in UC.

Methods: UC patients who underwent surveillance colonoscopy in 1996-7 were identified from a gastrointestinal pathology database and included if they had UC ≥ 7 years, ≥ 2 surveillance exams, and no histologic dysplasia at entry. Data were abstracted from subjects' medical histories, colonoscopy and pathology reports. Proportional hazards analysis was performed to evaluate the effect of 6MP use over time on the endpoints: (a) progression to any neoplasia and (b) progression to advanced neoplasia. Life table analysis tested for the influence of covariates, including mesalamine use.

Results: 315 subjects met inclusion criteria. There were no significant differences in rates of progression to advanced neoplasia or any neoplasia between 6MP-users and never-users by log-rank testing. Proportional hazards analysis resulted in hazards ratios of 1.06 (95% CI: 0.59 – 1.93) and 1.3 (95% CI: 0.45 – 3.75) when considering the effect of 6MP-use on progression to any or advanced neoplasia respectively. Results were unaffected by known potential confounders.

Conclusion: In UC patients without history of dysplasia, 6MP/AZA use appears to have little to no effect on rate of colonic neoplastic transformation. Importantly, the use of 6MP/AZA did not increase malignant transformation in UC.

Characterization of alpha-Galactosidase A Signal Peptide Mutations. M. McCarthy, G. Thiagarajan, M. Yasuda, J. Shabbeer, and R.J. Desnick. Department of Human Genetics, Mount Sinai School of Medicine, New York, NY.

Fabry disease is an X-linked recessive inborn error of glycosphingolipid catabolism results from deficient activity of the lysosomal exoglycohydrolase, alpha-galactosidase A (alpha -Gal A). The signal peptide of the alpha-Gal A gene consists of 31 amino acids that direct the protein to the endoplasmic reticulum for subsequent trafficking to the lysosome. Generally, the signal peptide motifs consist of: one of the first five residues of the N-terminal region contains a basic amino acid followed by a central hydrophobic core, an a-helix breaker – 4 to – 8 residues from the cleavage site, and a C-terminal signal cleavage site with a sequence of Ala-X-Ala. Five alpha-Gal A signal sequence mutations (M1R, M1T, M1I, A20P, and still in progress A31V) were characterized by over expressing their respective mutant enzymes in COS-7 cells. Mutations were introduced by site-directed mutagenesis. The sequence-confirmed mutant alpha-Gal A constructs in the expression vector pcDNA3 were then transiently transfected into COS-7 cells, and the intracellular and secreted enzymatic activity was analyzed using a specific fluorogenic substrate. Mutations of the first Met residue in the protein resulted in negligible enzymatic activity, while A20P had ~4% of wild-type activity. Immunofluorescence microscopy using specific anti-alpha-Gal A antibodies demonstrated that M1R, M1T, and M1I proteins were not detectable in the endoplasmic reticulum, Golgi apparatus, or endosome/lysosome system, indicating that these polypeptides were rapidly degraded in the cytosol. In contrast, the A20P mutant demonstrated lysosomal staining, although markedly reduced as compared to wild-type. Apparently, the proline 11 residues upstream of the cleavage site had a less deleterious effect on inevitable delivery of the enzyme to the lysosome as compared to mutations at the first methionine residue. These studies demonstrated that signal peptide mutations in alpha-Gal A, with the notable exception of A20P, were unable to enter the endoplasmic reticulum and rapidly degraded in the cytosol, thereby causing classical Fabry disease.

Construction and Expression of an NUP98-NSD1 Fusion Gene, a Novel Gene Product Implicated in Childhood Acute Myeloid Leukemia (AML), and Investigation into Deregulation of Set-Domain Histone Lysine Methyltransferase Activity. I.J. Neeland and J.D. Licht. Gerald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY.

The novel gene products of NUP98-NSD1 and MMSET have been implicated in human malignancy. Recent research has demonstrated that NSD1 and possibly MMSET contain a SET-domain sequence of amino acids that possesses histone lysine methyltransferase (HMTase) activity, an important regulatory mechanism of DNA transcription and gene expression. Deregulation of this process may be a contributing factor in oncogenesis. Investigation into the action and regulation of these proteins is required in order to understand their role in deregulation of transcriptional control leading to malignancy. Our specific aims were to: (a) Create an expression construct of NUP98-NSD1 using PCR amplification techniques. (b) Express the construct in cells with the purpose of studying its expression and gene activity using Western blotting and immunofluorescence. We hoped to compare the fusion construct with a non-fused NSD1 protein. and (c) Overexpress the MMSET protein in a human cell line and compare its effects on cellular proliferation with wild type cells. At present, cloning protocols to engineer the fusion gene have been successful (Aim 1) and we expect to have a finished clone with which to use in expression assays soon (Aim 2). MMSET was successfully transfected into NIH/3T3 cells and protein expression levels were quantified using Western blotting. A colony-suppression assay is being performed to determine the effects of MMSET overexpression on cell growth (Aim 3). Understanding the HMTase activity of the SET-domain in NSD1 and MMSET will allow us to use it as a therapeutic target in the treatment of acute myeloid leukemia and multiple myeloma.

Motor and Sensory Neuropathy in Lead Poisoning: a Revision of the Classical Clinical Presentation of Workers Exposed to Lead. P.J. Neuburger and D. Milek. Mount Sinai-Irving J. Selikoff Clinical Center for Occupational and Environmental Medicine, Mount Sinai School of Medicine, New York, NY.

Despite substantial decreases in the number of instances of adult occupational lead poisoning, New York City currently experiences about 100 new cases per year. The decline in reported lead toxicity from occupational exposures has resulted in fewer studies of lead-related pathology and less discussion about the clinical presentation of lead toxicity. The classical description of lead poisoning taught for years in internal medicine, occupational medicine and neurology textbooks and on the wards describes an almost exclusively motor neuropathy. Five recent cases involving bridge painters with elevated blood lead levels and signs and symptoms expanding on the textbook description of lead toxicity have prompted us to reconsider the clinical presentation commonly associated with lead poisoning. We found substantial support for our clinical findings confirmed by a review of 33 studies describing sub-clinical changes in nerve conduction velocities (NCV) of both motor and sensory divisions of the peripheral nervous system after exposure to high levels of lead. Based on the results of our clinical assessment, laboratory testing and evidence in the literature, we believe that sensory deficits in the extremities should be evaluated during clinical examination of patients with lead exposure in addition to the motor deficits currently considered. This would serve to modify the practice of primary care, occupational medicine and the education of occupational physicians, internists, physician's assistants and nurses. It would also improve the quality of care given to patients with elevated blood lead levels

Designing a Cumulative Exposure Matrix for NYC Firefighters Exposed to World Trade Center (WTC) Dust. A.L. Nowak[1], G.L. Banauch, MD[2], K.J. Kelly, MD[2], and D.J. Prezant, MD[2]. [1]Mount Sinai School of Medicine, New York, NY and [2]the New York City Fire Department's Bureau of Health Services, Albert Einstein College of Medicine, Pulmonary Division.

A comprehensive analysis of health outcomes for the nearly 11,000 NYC firefighters at World Trade Center Ground Zero requires a cumulative exposure matrix encompassing the entire rescue/recovery/cleanup effort from 9/11/2001 to 6/30/2002. Two sources were used to identify firefighters present and their hours worked at Ground Zero—computerized fiscal records and handwritten supervisor records for each shift. After entering supervisor records into a computerized database, we compared supervisor and fiscal databases for matches in identity (firefighter name) and monthly work hour totals. Preliminary analysis for 2 months is reported. Our initial bias had been that fiscal records would be more accurate. After interviewing fiscal administrators, supervisor chiefs and firefighters, we found that fiscal records over-reported exposures both for numbers of firefighters present and hours worked at Ground Zero, as payroll codes were for operations related to WTC, but not actually taking place within the Ground Zero exposure perimeter. Supervisor work records provided a more accurate account of Ground Zero exposure, but firefighter identity and hours were frequently missing from the fiscal file because payroll codes were for regular firefighting duties. After completing these 2 databases, our next step will be comparison to the WTC medical-exposure database. A final cumulative exposure matrix will then be constructed for future health outcomes analyses.

Date	Fiscal Database	Supervisor Database	Identity Matches	Total Work Hours	Matches
11/01	972	968	217 (22%)	2	(0.2%)
06/02	160	106	59 (37%)	21	(13%)

Understanding the Motor Impairment after Stroke: Stretch-Dependent Weakness in Hemiplegia.

H.J. Park, D. Weisz, PhD, and J-M Gracies, MD, PhD. Department of Neurology, Mount Sinai School of Medicine, New York, NY.

Patients with hemiplegia share a clinical feature called spasticity, which is an increase in reflex responses to stretch at rest. It is not established whether and how such abnormal sensitivity of stretch receptors may also impact descending motor command. Twelve patients with hemiplegia (age 43±13, 7F) and twelve healthy controls (age 50±8, 3F) performed maximal voluntary isometric elbow flexions and extensions in two positions: elbow flexed at 100° and at full extension minus 10°. Mean Rectified Voltage (MRV) from surface agonist and antagonist electromyograms was measured over 500 ms of maximal contraction. In the paretic arm, there were trends for marked decreases in agonist recruitment when the elbow was extended, both in the flexors (−38%, p=0.06) and in the extensors (−38%, p=0.27). Co-contractions were significantly greater than in healthy controls during all efforts. Flexor co-contraction increased when the elbow was extended, whereas extensor co-contraction was unchanged. To reflect motor command quality we calculated a Coefficient of Efficiency (CE) [Agonist MRV - Antagonist MRV] for each effort in each elbow position. Normalized to healthy dominant arm, the CEs of elbow extension and flexion in the paretic arm were 8% and 12% respectively, in the flexed position vs. 1.5% and 6% respectively, in the extended position. Our results indicate that tonic recruitment of stretch receptors in the elbow flexors impairs motor command for both flexion and extension. This may suggest the need for lengthening interventions of this muscle group to improve reaching function in hemiplegia.

Apoptosis Signals Are Activated Immediately after Subarachnoid Hemorrhage.

F.M. Patterson, F.A. Sehba, and J.B. Bederson. Department of Neurosurgery, Mount Sinai School of Medicine, New York, NY.

Approximately 30,000 North Americans suffer from subarachnoid hemorrhage (SAH) each year and it accounts for 5–10% of all stroke cases. Acute (≤48 hours) ischemic brain injury is associated with most deaths after SAH. Death of neurons and endothelial cells via apoptosis is observed both in human and experimental SAH. The present project is designed to study the temporal profile of activation of apoptosis during the first 48 hours after experimental SAH. SAH was induced in the rat using the endovascular filament model. Animals were sacrificed 10 minutes, 1, 3 or 6, 24 or 48 hours after SAH. Time matched shams were used as controls. Adjacent 8 um brain sections immunostained for caspase-3 and DAPI were used to detect apoptotic cells. Caspase-3 and DAPI immunofluorescence examined in frontal and dorsal cerebral cortex, striatum and hippocampus and dual labeled cells were counted. An increase in dual labeling with time delineates cells undergoing apoptosis. In this ongoing study so far we have observed the presence of caspase-3 labeling in the brains of animals sacrificed 3 hours after SAH. Dual DAPI labeling of caspace-3 positive cells indicated nuclear deformity confirming an apoptotic event. These results indicate that apoptotic signals are activated early after SAH.

Needs Assessment Study Establishing a Scientific Study of Siddha Medicine Treatments of HIV/AIDS.

D. Pooran, N. Hennig, MD/PhD, K. Baban, S. Ikeda, and H. Sacks MD/PhD. Thomas C. Chalmers Clinical Trials Unit, Mount Sinai School of Medicine, New York, NY.

Gandeepam is a non-governmental organization in Tamil Nadu, South India utilizing Siddha medicine, an ancient East Indian tradition, to treat HIV/AIDS. The goal of the assessment was to set up an objective study of Siddha medicine's treatment of HIV/AIDS patients. India has the third highest HIV/AIDS infection rate in Asia and Tamil Nadu has 44.7% of the AIDS cases in India (Population Foundation of India, 2000). Despite the Indian government's attempt to provide free ARVs, many patients have no access to treatment and depend on traditional healers for care. Siddha practitioners suggest that their treatment is most effective for WHO's Stage 1 & 2 HIV/AIDS patients, thereby adding to rather than replacing ARV therapy. Therefore, a scientific examination of the effectiveness of Siddha treatments will be beneficial. The assessment included investigation of a Siddha clinic, a Siddha hospital, and several clinical laboratories. The primary finding was the need for two independent laboratories to conduct ELISA, Western Blot, CD4/CD8, and HIV Viral Load tests in order to evaluate the Siddha diagnosis and how HIV/AIDS patients progress through treatment. The Meenakshi Mission Hospital Laboratory and Lister Metropolis Clinical Laboratories are able to conduct reliable blood tests of the study subjects. Another significant finding was the need for a locked file cabinet in which to maintain the confidentiality of patient records (consent, name/address, picture, etc.). However, more work needs to be done to ensure patient safety and confidentiality in examining the effectiveness of Siddha medicine treatments.

Improving Breastfeeding in East Harlem: Developing an Appropriate and Sustainable Curriculum for Breastfeeding Educators in the Mount Sinai And East Harlem Communities.

C.L. Quinn, E. Garland, and J. Rethy. Department of Community Medicine and Preventive Health, Mount Sinai School of Medicine, New York, NY.

This project created a sustainable breastfeeding curriculum for health care providers in the Mount Sinai community, through collaboration with lactation consultants from Maternal Child Health and community-based providers. Current curricula for breastfeeding education directed at Mount Sinai residents in Ob/Gyn and Pediatrics, medical students, and community health educators such as WIC nutritionists were surveyed and evaluated. Breastfeeding outreach in the community was observed at Mount Sinai breastfeeding classes and support groups and WIC office visits. The information obtained from observation and evaluation was used in collaboration with lactation consultants to identify topics for inclusion in breastfeeding curricula. A thorough review of current breastfeeding literature was conducted. New curricula appropriate to each group of providers were developed, consisting of PowerPoint presentations with fully referenced notes for presenters. This project resulted in materials for sustainable, appropriate breastfeeding education to providers in the East Harlem community. A pre- and post-test with content questions was developed for the purpose of evaluating the curricula.

Background: Research in recent years has proven the benefits of breastfeeding. The Healthy People 2010 report from DHHS set a target for breastfeeding initiation of 75%. However, breastfeeding rates, particularly among women on Medicaid, remain low. In 2000, only 20% of mothers on Medicaid discharged from Mount Sinai were breastfeeding exclusively. There is currently no formal curriculum for health care providers at Mount Sinai or community-based groups for providing breastfeeding counseling and support. In order to improve breastfeeding, all providers should be trained in breastfeeding counseling and solving common problems.

Food Availability in the Urban Environment of East Harlem. C.J. Raines and M.P. Galvez, Department of Community and Preventive Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY.

According to the New York City Department of Health, 43% of New York City children are overweight. Poor diet is a major risk factor for obesity. Yet, little is known about how the physical or "built environment" impacts children's dietary habits. "Growing Up Healthy In East Harlem," a community-based participatory research project, will address the environmental determinants of childhood overweight unique to the urban built environment of East Harlem. A survey of East Harlem zip codes 10029 and 10035 was performed through (a) direct observation via walking tours of the neighborhoods and (b) compiling information from the New York State Department of Agriculture. A series of maps depicting the food environment of East Harlem has been developed using the geographic information systems software package, ArcGIS. These maps illustrate food sources (fast food stores, restaurants, bodegas, supermarkets, and specialty stores) and their proximity to schools and neighborhood housing. These data highlight the limited availability of high quality fresh fruits and produce and the abundance of food stores with unhealthy foods located in this community. Further analysis will examine baseline demographics of the East Harlem community, and how availability, proximity and density of resources impact diets of East Harlem children. Maps will also serve as a community resource in order to highlight healthy food stores in East Harlem. The implications of this study include the need to address factors at both the individual level when recommending dietary changes and at the community level when addressing deficiencies in the local food environment.

Internalized Homonegativity and Unsafe Sex in MSM. P. Saadai, BA, F. Muench, MA, and J. Morgenstern, PhD. Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Background: Previous research has identified internalized homonegativity (IH) in gay men and women as a correlate with indicators of psychological distress, such as depression, anxiety, or poor self-esteem. It has been hypothesized that IH is related to behaviors with important clinical consequences such as unsafe sexual behavior, although results have been mixed.

Objective: The aim of this study is to examine the relationship between Internalized Homonegativity and unsafe sexual behavior in a population of men who have sex with men (MSM).

Methods: Participants were 183 MSM from the New York City area who self-identified as sexually compulsive and completed a one-time survey which assessed unsafe sexual practices and IH. The relationship between IH and sexual risk taking was analyzed.

Results: IH scores of our sample on the IHNI scale were analyzed in comparison to a normative sample ($n=241$). The compound IH score in our sample of SC MSM score was significantly higher $t(182)=3.385$, $p<0.001$ A one-way ANOVA comparing those who had and had not engaged in unprotected anal sex on >2 occasions over 90 days prior to assessment showed that there was a significant mean difference on the IH scale between these two groups, $F=5.81$, $p<0.01$. Finally, a Pearson Correlation between overall IH and SC on the YBOCS scale revealed a weak significant correlation, $r=1.93$, $p<0.01$.

Conclusion: Findings regarding the relationship between increased IH and unsafe sexual behavior have important clinical implications for the treatment of gay men as well as in HIV and STI prevention and treatment in this population

A Survey of International Disaster Mental Health Services. S.H. Sanchez and C.L. Katz, MD, Director, Acute Care Psychiatric Services, Mount Sinai Hospital, New York, NY.

Disasters' effects on survivors, the families of victims, emergency workers, and the affected community can be devastating. The response to disasters must be multi-dimensional, including provision for food and shelter, attention to medical needs, and reinstitution/revision of the destroyed infrastructure. Yet, it is believed that immediate and long-term mental health concerns are either ignored or assigned low priority. This project surveyed 196 English-speaking, international non-governmental agencies (NGOs) as listed on the United Nations website, www.reliefweb.int, to determine to what extent this observation is true at the international level. Primary information was drawn from websites (with no technical difficulties), although direct contact by email was utilized in some cases t supplement website information. NGOs were included for analysis if thei mission/vision statement(s) revealed agency goals that could reasonabl be interpreted to encompass mental health. Of the 196 surveyed, 11 agencies/NGOs were included for further analysis. Major criteria examined include whether each agency mentioned any international relief/development program that addresses mental health concerns (62); existenc of within-agency mental health staff, volunteers, or consultants (30); existence of procedures for implementing disaster-related mental servic (19). All 196 agencies/NGOs reviewed were included in determinin whether there were existing mental health services for their own staff (5) Given the prevalence of untreated mental illness worldwide and the likel adverse impact that crisis situations have on this baseline, the scarcity o disaster mental health and mental health development services among international NGOs appears to be a matter of concern for policy-making.

The Extent of Integrated Pest Management Adoption in the Eas Harlem Community as an Alternative to Traditional Pest Control N.A. Schmelzer, G. Rosenberg, and B. Brenner. Department of Community and Preventative Medicine, Mount Sinai School of Medicine, New York, NY.

Growing Up Healthy in East Harlem, a community intervention study 1998 – 2003, recognized the relationship between health status and housing environments of East Harlem residents, and a need for affordable, safe and effective pest control services, with community education, to reduce risk factors for asthma and exposure to neurotoxic chemicals among children. It was demonstrated that Integrated Pest Management (IPM) was effective in reducing household cockroach infestation and the use of chemical pesticides. This project investigated the types of pest control methods currently available to households in East Harlem, in order to determine the extent of IPM adoption and to highlight barriers to its adoption. Twenty-one businesses and community intervention projects which provide pest control services in East Harlem were identified and contacted. Eight responded. Many businesses refused to be surveyed regarding their pest control practices. Of those willing to discuss their techniques, all had universally adopted the term IPM to describe their preferred method of pest control, although their specific practices were widely inconsistent. Overall, only three of the eight providers surveyed strictly adhered to complete IPM procedures. The other five reported barriers to strict IPM implementation, such as lack of resident education, cost, and poor sanitation and maintenance. IPM must be applied within East Harlem in a manner that is consistent, effective and reliable. Guidelines following a uniform procedure for IPM should be established, with licensed exterminators held to this standard. Additionally, residents should be made knowledgeable about safe pest control practices so they can act as informed consumers.

Normal Morphology of the Human Cerebellar Vermis in vivo: an MRI Evaluation of the Angular Relationships among the Vermian Lobules. M.B. Schwartz, BA, and T.P. Naidich, MD, FACR. Department of Radiology, Mount Sinai School of Medicine, New York, NY.

Background: Recent neuroimaging studies have provided qualitative data on the changes in normal vermian morphology with age and gender, and on pathologic changes in vermian morphology in autism, schizophrenia, ethanol abuse, and congenital malformations. Quantitative data on vermian areas and volumes are sparse, inconclusive or frankly contradictory. To our knowledge, there have been no studies to provide quantitative normative data on the orientation and angular interrelationships among the individual lobules.

Hypotheses: (a) Measurement of the radial pattern of the vermian white matter (arbor vitae) on T2-weighted midsagittal magnetic resonance images (MRI) will establish normal ranges of lobar orientations and angular interrelationships among the vermian lobules. (b) These relationships will show limited reproducible variations with age and gender.

Methods: Retrospective analysis of midsagittal T2-weighted MRI's was performed for 100 male and 100 female patients, distributed evenly across all decades of age, whose studies were interpreted as "within normal limits." The angles among the branches of the central digitations of white matter to each lobule were measured directly from the computer images and correlated with standard measures of angles and lengths of the skull base and midline brain parenchyma.

Results: Preliminary results indicate that the angular relationships among the vermian lobules are highly consistent and independent of age and gender in all patients older than ten years. **Conclusion:** This study proves the two hypotheses correct. These normative data are expected to serve as baseline for the future study of vermian pathology.

Ultrasound Technology in Assessing Anisotropic Loss in Osteoporotic Trabecular Bone. S.S. Seo, L. Cardoso, K. Jepsen, and M.B. Schaffler. Orthopaedic Research, Mount Sinai School of Medicine, New York, NY.

Ultrasound (US) is a rapidly developing technology widely used for measuring bone density and assessing bone loss in patients. Like bone densitometry, US is currently limited because it does not consider directionally specific changes in microarchitecture when bone becomes osteoporotic. However, unlike bone densitometry, the US signal contains microarchitectural information, which if accounted for properly can improve prediction of bone strength and fracture risk. In the current study we examined cancellous bone samples obtained from Dr. Schaffler's NASA/NSBRI studies of immobilization-induced bone loss and treatment with bisphosphonate antiresorptive drugs. Cancellous bone cubes from immobilized (IM) and bisphosphonate-treated (IM+BIS) animals were examined, as were samples from control and drug treated control animals. Ultrasound was used to assess bone mechanical properties in specific anatomical directions (SI, AP, ML). Additionally, a structural parameter accounting for volumetric orientation was determined using Biot's Theory. Quantitative changes in structure are being measured from micro CT images (studies ongoing). Among all groups, mechanical properties were significantly greater in the SI direction than in transverse directions. Both IM and IM+BIS bones showed significant losses in mechanical properties overall. However, immobilized bone lost the most mechanical integrity in the SI direction, while IM+BIS bone showed proportional loss in all directions. These suggest that anti-resorptive therapy maintained the normal cancellous bone anisotropy and structural scaffolding even with reduced bone mass, and should profoundly improve the recovery potential following normal use. Assessment of anisotropic properties of cancellous bone is possible using US, and should improve the diagnosis of bone diseases and effectiveness of bone therapies.

Barriers to Influenza Immunization in an Elderly Urban Population. R.M. Small and M.E. Foley, EdD, RN. Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Objective: In East Harlem, adult hospitalization admission rates for pneumonia and influenza are 90% higher compared to New York City as a whole. Influenza immunization rates remain below the Healthy People 2010 goal of 90% vaccination coverage of the elderly, with lowest immunization rates among minority populations. The purpose of this study was to identify barriers to influenza vaccination uptake in an elderly minority clinic population residing in Harlem and East Harlem, New York City.

Methods: Observational, cross-sectional, survey study. Using a face-to-face survey, patients (n=60) and providers (n=20) were interviewed at an urban geriatric clinic serving over 2500 elderly patients per year. The patient survey asked about demographics, general health, and perceived barriers to immunization. The provider survey elicited responses on immunization practices, vaccination management, and perceived barriers to immunization.

Results: Overall, 75% of the respondents were immunized for the last flu season. The most commonly reported barrier from all patients was the concern of getting influenza from the vaccine. Of those not immunized, 33% thought they would get the flu from the immunization. By ethnicity, 31% of African American patients believed the vaccine caused the flu; 23% of Hispanic patients were concerned about an adverse reaction. Cost and access to care were not barriers. Synthesized provider responses corroborated patient findings.

Conclusions: Despite practice initiatives to improve vaccination rates, immunization rates remain below the national objective. Community health care providers must increase awareness of the need for vaccination, address public misconceptions through patient education, and reduce missed opportunities for vaccination.

Combining Systemic Retinoids with Biologics for Moderate to Severe Psoriasis. E.C.A. Smith[1], C. Riddle, MD[2], M.A. Menter, MD[2], and M. Lebwohl, MD[1]. [1]Department of Dermatology, Mount Sinai School of Medicine, New York, NY and [2]Baylor University Medical Center, Department of Dermatology, Dallas TX.

Psoriasis affects approximately 2% of the population and often presents a therapeutic challenge to physicians. Patients with severe psoriasis often require combinations of systemic therapy to control their disease. Until recently, the only systemic therapies were methotrexate, cyclosporine, and acitretin. With the emergence of new biologic therapies, dermatologists now have a wider array of tools for use against this disease. The mechanism of action of the systemic agents commonly used differs from the newer biologics, suggesting that when combined, these therapies may have additive effects. Thus data is needed to determine the safety, tolerability, and efficacy of the biologic agents when added to the other systemic therapies. There is little experience with acitretin and biologics. The aim of this study was to ascertain the efficacy, safety, and tolerability of acitretin when combined with biologic agents for moderate to severe psoriasis. To determine this, patients with psoriasis who were treated with acitretin and a biologic were identified and their charts retrospectively reviewed. Of the 14 patients treated with acitretin and a biologic, four patients cleared, six patients improved 90%, two improved 75%, one improved 50%, and one had no change. During treatment with acitretin and biologic, five patients required no adjunctive treatment. Three patients were able to stop narrowband UVB therapy after an average of 2.33 months of combination therapy. Only one patient continued to need phototherapy (UVB) after addition of the biologic. Thus, acitretin combined with biologics offers a promising method of managing refractory psoriasis.

Risk Factors for Increasing Aortic Intima-Media Thickness among the Elderly. A.E. Soumekh, M.E. Goldman, and L.B. Croft. The Zena and Michael Weiner Cardiovascular Institute, Mount Sinai Medical Center, New York, NY.

Studies have shown that carotid intima-media thickness is an excellent marker of subclinical atherosclerosis. Little research has focused on thoracic aortic intima-media thickness and its relationship to cardiovascular risk factors and coronary artery disease. The purpose of our study was to use transesophageal echocardiography (TEE) to determine the risk factors for aortic intima-media thickening (aIMT) and identify a correlation between increasing IMT and coronary artery disease (CAD). The study population consisted of 55 patients (mean age = 66 yr, range 21 to 93) referred to Mount Sinai Hospital's Non-invasive Cardiology Laboratory for a TEE. Each patient's demographics, cardiovascular risk factors and pertinent medical history were recorded. After completion of the TEE with a 7.5 MHZ probe, an echocardiologist blinded to the results of the patient's information identified and measured aortic plaque morphology and thickness and IMT. Among all patients, significant increases in aIMT were seen with diabetes (0.146 cm, $p<0.05$), hyperlipidemia (0.133 cm, $p<0.01$) and hypertension (0.184 cm, $p<0.01$). Increased IMT also correlated with CAD: subjects with CAD had an average of 0.156 cm greater aIMT ($p<0.01$). Subgroup analysis of patients over 65 years old showed similar trends in diabetes (0.145 cm, $p<0.05$), hypercholesterolemia (0.037 cm, $p>0.05$), hypertension (0.147cm, $p>0.05$), and CAD (0.070 cm, $p>0.05$). Therefore, our pilot study demonstrated that increased aortic IMT is associated with cardiovascular risk factors and CAD, irrespective of age. Increased aortic IMT may be a marker of diffuse vascular disease with manifestations in the coronary, cerebral and vascular circulation.

Computational Meta-analysis of Quantitative Trait Loci (QTLs) and Microarray Gene Expression Databases to Generate Composite Genomic and Transcriptomic Renal Disease Maps. K.V. Star and E.P. Böttinger. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Quantitative trait locus (QTL) is a polymorphic locus containing alleles that differentially affect the expression of a specific phenotypic trait. The purpose of QTL research is to find the genes underlying these traits. QTLs have been mapped in inbred species: rodents, plants, and insects. Despite this progress, finding the genes underlying quantitative traits remains a challenge. We use a combination of microarray data, human genome linkage, QTLs, and comparative genomics to find new genes and pathways associated with common human diseases. In order to move from QTLs to genes we have generated a comprehensive QTL database of *Mus musculus*, *Ratus norvegicus* and *Homo sapiens* using data from PubMed, Online Mendelian Inheritance in Man, UCSC Genome Browser, Mouse Genome Informatics and Rat Genome Database. To make this tool available to the research community, we have developed a user interface for high throughput mapping of genes to QTL regions. Currently the database is mined for genes from microarray experiments of kidney disease mouse models generated in our laboratory and ENU mutagenesis datasets. As we found that the majority of quantitative trait loci map to syntenic blocks, comparative genomics is used to narrow these QTL regions and to decrease the number of candidate genes. Focusing on renal diseases, we illustrate how the use of innovative genetical genomics strategies may facilitate disease gene discovery.

Nursing Assistants as Observers of Behavior and Medication Administration in a Nursing Home Setting. H.L. Takusagawa, B. Fridman, MD, and K. Boockvar, MD, MS. Brookdale Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

Certified Nursing Assistants (CNAs) provide up to 90% of the direct care received by a nursing home resident. Past studies have revealed that increasing CNA involvement in the clinical decision making team could increase CNA job satisfaction and decrease turnover rate. This study examined the reliability and validity of CNA observations of residents' behavior, mood, physical functioning, and medication administration. We developed a survey of questions derived from the Minimum Data Set (MDS), a federally mandated quarterly resident assessment. Our survey was administered to the nurses (n=17) and CNAs (n=26) of 29 residents diagnosed with dementia or depression living in the Jewish Home and Hospital, a 500-bed academic, urban nursing home. Nurse and CNA responses were compared to each other as well as to recorded data from the resident's current actual MDS and nursing Medication Administration Record (MAR). Agreement was ascertained using the kappa statistic, a measure of agreement beyond that expected by chance. CNA reports of behavior, mood, and physical functioning had good (kappa 0.44–0.79) and variable (kappa 0.16–0.68) agreement with nurses and the actual MDS, respectively. Agreement between CNA reports of drug administration and the MAR was poor (kappa 0.00–030). Good agreement between CNAs and nurses suggests that CNAs' observations of residents' psychological and physical function are reliable and fairly accurate. CNAs may occupy a unique niche in which they can provide naturally blinded assessment of symptomatic response to drug treatments, without bias from awareness of actual medication administration.

A Retrospective Study on the Long-Term Efficacy of Acetylcholinesterase Inhibitors (AChEI) on the Course of Alzheimer's Disease (AD). J.Y Tang, A. Atri, MD, J.J. Locascio, PhD, L. Yap, PhD, and J.H. Growdon, M.D. Alzheimer's Disease Research Center (ADRC), Massachusetts General Hospital, Boston, MA.

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to dementia, resulting in cognitive, functional, and behavioral disturbances. As the chief biochemical abnormality in AD is impaired acetylcholine neurotransmission, short-term therapy for managing AD patients involves augmenting neurotransmitter activity by inhibiting the enzymatic hydrolysis of acetylcholine with AChEIs. These drugs have been shown to improve symptoms in clinical studies ranging from six months to a year, but there are limited data on their long-term efficacy. To correct this gap in information, we compared the mean slope of decline in AD patients treated with AChEIs (n=448) to the decline in untreated patients (n=310). We hypothesized that treatment would produce a shallower slope. A retrospective design was used, selecting from the MDC ADRC database probable AD patients treated with AChEI between 1998 and 2003, and a comparison group from between 1990 and 1995, before the introduction of AChEIs. Linear regression analyses and Student t-tests were used to compare the rates of change on a cognitive measure, the Blessed Dementia Scale (BDS), and a functional measure, Activities of Daily Living (ADL), between the two groups. Performance on BDS of the untreated group deteriorated by 4.4±0.3 points per year vs. 3.0±0.3 points per year in the treated group (p=0.001), favoring AChEI therapy. There was no significant detectable effect on function (p=0.11). Our findings indicate that AChEIs lessen the slope of cognitive decline in AD, and support their use beyond one year of treatment.

A Volumetric MRI Study on Impulsive Aggressive Patients with Borderline Personality Disorder. R. Trisdorfer, A.S. New, R. Newmark, E. Hazlett, and M. Buchsbaum, Department of Psychiatry, Neuroscience PET Laboratory, Mount Sinai School of Medicine, New York, NY.

Background: Patients with borderline personality disorder (BPD) frequently suffer from impulsive aggression (IA), which poses a serious threat to themselves and others. MRI studies have shown decreased brain volume in the amygdala, hippocampus, frontal lobe, and cingulate in patients with BPD.

Methods: Sixteen controls (9 male, 7 female) and 14 BPD patients (10 male, 4 female) with IA, age- and sex-matched, underwent MRI imaging. While blinded to subject diagnosis, coronal images of the brain were outlined and volumes calculated using a computer program delineating Brodmann areas (BAs). Gray matter volume relative to whole brain volume in BAs in the frontal cortex and cingulate gyrus were evaluated with STATISTICA.

Results: In the frontal cortex, volume was entered into a group (BPD, NC) x region (dorsal, medial, orbital) x BA (44, 45, 46; 9, 24, 32; 11, 12, 47) x hemisphere (R, L) mixed factorial ANOVA, no significant interactions were found. With sex as an additional grouping variable, female BPD patients showed a significant increase, and male patients a decrease in gray matter in the medial frontal cortex (BAs 9, 24, 32) compared to controls (F(2, 52)=4.78, p<0.02). In the cingulate gyrus, volume was entered into a group (BPD, NC) x BA (25, 24, 31, 23, 29) x hemisphere (R, L) mixed factorial ANOVA, no significant interactions were found. Using sex as an additional grouping variable, in the right cingulate (BA 31), female BPD patients showed an increase, and male patients showed a decrease in gray matter (F(4, 104)=2.6, p<0.04).

Conclusions: Male BPD patients with IA show decreased gray matter in the medial frontal cortex and right cingulate, supporting the results of previous volumetric MRI studies. Future studies coregistering the MRIs to PET scans will be undertaken to assess differences in brain activity.

Hopelessness as a Marker for Trauma-Related Distress in Primary Care Pediatrics. A. Tzavaras, D. Steinbaum, and D. Laraque. Division of General Pediatrics, Mount Sinai School of Medicine, New York, NY.

Backgound: Currently available psychosocial screening tools used by pediatricians do not screen for trauma-related distress.

Objective: We hypothesize that the presence of hopelessness can function to identify trauma-related distress in an inner city population of children. Specifically, this study will assess the sensitivity and specificity of a single hopelessness question used in a currently available psychosocial screening tool to identify children with symptoms of trauma-related distress.

Methods: A cross-sectional psychosocial study of 300 patients is being conducted at the Pediatric Associates Practice, Division of General Pediatrics of Mount Sinai Medical Center in New York City, looking at psychosocial dysfunction. We report the results of 66 patients, ages 8-10.

Results: Preliminary data reveal that the "hopelessness question" detected 89% of children in need of further evaluation for trauma.

Conclusions: Hopelessness in this inner city population of children is associated with the presence of trauma-related distress.

Estimation of the Prevalence of Epilepsy in the Multiethnic Community of Washington Heights/Inwood, New York City, 2003. L. Ungsunan and D.C. Hesdorffer. Gertrude H. Sergievsky Center, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

Several studies have examined the prevalence of epilepsy in relatively homogenous populations, but few studies have investigated its prevalence in ethnically diverse communities. Previous reports suggest that minorities have a higher prevalence of epilepsy (1–3), but fall short of providing detailed information on ethnicity, seizure type, and etiology. In light of this gap in knowledge, this study intends to estimate the prevalence of epilepsy in Washington Heights/Inwood, NYC, where a majority of residents are Latino or African-American. Prevalent cases of epilepsy were identified after reviewing admission and discharge diagnoses, medical record notes, or imaging/EEG results for patients attending the New York Presbyterian Hospital Emergency Departments (NYPHED) and the Allen Pavilion Emergency Department. Review was restricted to residents of zip codes 10031–10034 and 10040. This numerator is expected to underestimate the number of prevalent cases in the community, since patients with epilepsy may seek care elsewhere. Therefore, we plan to apply capture-recapture methodology (CRM), using all NYPHED contacts during the 6-month study period to estimate the denominator population reported by the 2000 U.S. Census. If this method gives an accurate estimate of the denominator population, CRM will then be used to estimate the numerator for prevalence, based upon the identified cases and cumulative patient visits. If CRM fails to estimate the denominator population, then the prevalence of epilepsy in the NYPHED alone will be calculated. By advancing our knowledge of the burden of epilepsy in a diverse, urban community, this study will provide the basis for future resource development and intervention planning.

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Effects of Low-Carbohydrate Diets on Cognitive Functions. B.R. Vaughan, C.V. Mobbs, and F. Isoda. Fishberg Neurobiology of Aging Laboratories and Brookdale Department of Geriatrics, Mount Sinai School of Medicine, New York, NY.

Despite widespread interest in low-carbohydrate diets, surprisingly few studies have actually examined the effects of low-carbohydrate diets in animal models. Dr. Mobbs' laboratory has shown that a low-carbohydrate Atkins-type diet does not reverse obesity in laboratory mice. However, the Atkins-type diet is relatively high in protein and it may not actually cause ketogenesis by itself. In fact, recent data from Dr. Mobbs' laboratory suggests that a true ketogenic diet (used to treat epilepsy), which is relatively low in protein as well as carbohydrates, may in fact be useful to reduce obesity. However, some evidence suggests that ketogenic diets may impair certain cognitive functions. A plausible mechanism for these impairments is that ketogenic diets may reduce epilepsy by interfering with excitatory amino acid transmission (especially glutamate release), and it is well-established that interference with the glutamate system in particular may produce cognitive impairments. Nevertheless, effects of ketogenic diets on cognitive function and the glutamate system have not been examined in detail. We have now examined the effects of the ketogenic diet on memory function, using spontaneous reversal on a T-maze, and that memory function if mice were on the diet less than one month. However, we did find that the diet increased body temperature significantly. This observation suggests that the ketogenic diet may facilitate weight loss by increasing metabolic rate. We are currently assessing memory functions in mice on the ketogenic diet for more than one month.

Survey Investigating the Association between Internet Use and High Risk Sexual Behavior among Men Who Have Sex with Men. C.M. Vaughn and Dr. S.E. Goldstone. Mount Sinai School of Medicine, New York, NY.

Recently, there has been a troubling rise in the incidence of STDs among men who have sex with men (MSM). Past studies have linked outbreaks to Internet chat rooms. While studies have been done, there has been no substantial research to determine why the Internet has become a popular place for MSM to meet other men. In addition to answering that question, I also wanted to discover if MSM thought of Internet "hook-ups" as risky, and if risk behavior varied depending on the venue in which MSM meet each other. I also wanted to see patterns of drug use during sex. I created a survey that was given to 300 MSM by myself and filled out anonymously. The survey was also placed online at gayhealth.com, where it was filled out by an additional 300 men. While work still needs to be done, based on preliminary data, 65% of MSM who filled the survey out online meet people online for sex. Of those, 54% did drugs during their last sexual experience. Thirty-five percent who rated meeting people online for sex as risky were still willing to engage in risky sexual behavior. After further development, the results of this survey will provide useful information for public health officials trying to reduce STD risk among MSM and create more effective methods of preventive outreach.

Pur-Alpha Functions in RNA Targeting to Dendrites. D.B. Weinreb and E.M. Johnson. Department of Pathology, Mount Sinai School of Medicine, New York, NY.

The Pur protein family in humans consists of four members which are highly conserved throughout evolution. The first Pur family member to be identified, Pur-Alpha, interacts with both single-stranded DNA and RNA and has been implicated in recruitment of regulatory proteins during DNA replication, gene transcription and RNA transport. Genetic inactivation of mouse PURA causes defects in brain development and death. The association of Pur-Alpha with BC1 RNA, implicated in targeting mRNA for translation in dendrites, strongly suggests a similar role for Pur-Alpha. Recent studies have described a protein/mRNA complex from the mouse brain containing Pur-Alpha, BC1 RNA, the fragile X mental retardation protein (FMRP) and Staufen, the latter two of which are involved in translation and RNA transport respectively. Presently, we have used immunoflorescence cytochemistry and confocal laser microscopy to examine the presence of Pur-Alpha, FMRP and Staufen in embryonic day 18 rat hippocampal neurons grown in culture for 10–20 days. We have demonstrated that Pur-Alpha and Staufen are each present in the cell body and the dendrites, but not the axons, of cultured hippocampal neurons. Pur-Alpha levels peak in the dendrites on the sixteenth day of culture and decline at day 18. Furthermore, confocal microscopy has allowed us to co-localize Pur-Alpha in these neurons with FMRP and Staufen. Collectively, these results indicate an essential interaction between Pur-Alpha, Staufen, FMRP and MAP-2 in targeting mRNA to dendrites in developing hippocampal neurons. Future studies will employ RNA Immunoprecipitation (RIP) to identify mRNA molecules targeted to dendrites by these proteins.

Magnetic Resonance Imaging of Subclinical Atherosclerotic Disease: a New Quantitative Method to Evaluate Plaque Burden. K.B. Weinshelbaum, S.H. Aguiar, V. Mani, D.D. Samber and Z.A. Fayad. Imaging Science Laboratories, Mount Sinai School of Medicine, New York, NY.

The aim of this study was to use magnetic resonance imaging (MRI) to quantify the burden of atherosclerotic disease in extended areas of the aorta and carotid arteries. Cardiovascular events are clinical expressions of atherosclerosis resulting from long-term systemic pathology of arterial walls. MRI of subclinical atherosclerosis may provide an important and original quantitative profile of systemic disease in patients. Subjects at intermediate to high risk for cardiovascular disease (n=98, aged 55±20.4 years, range 9–87 years, 33% females) underwent high-resolution black-blood MRI of the aorta and extracranial carotid arteries. For each subject, cross-sectional images of the aorta (n=36–48) and carotids (n=12–24) were analyzed. Average arterial wall area (AWA), average wall thickness (AWT), and maximal wall thickness (MWT) were measured. Men had greater carotid AWT and MWT than women (2.3±0.7 vs. 2.1±0.6 mm, $p=0.0407$; 6.4±2.8 vs. 4.9±1.8 mm, $p=0.0039$), but there was no statistical difference when normalized to body surface area (BSA). Men had greater aortic AWA than women (153.5±64.7 vs. 128.2±55.8 mm2, $p=0.0291$), but when normalized to BSA there was no statistical difference. All carotid and aortic measurements increased with age ($p<0.0001$), and wall thickening was observed at earlier ages in the aorta than in the carotids. Aortic AWA normalized to BSA showed high correlation with age (R-squared=0.4397, $p<0.0001$). Black-blood MRI may be a useful, non-invasive method to quantify burden of atherosclerotic disease in patients. This project may establish the basis for further population studies on risk stratification and for guiding treatment in primary prevention of cardiovascular events.

Analysis of Bone Resorption in the Human Femur. J.C. Williams, M.A. Cordova, D.C. Casagrande, J.E. Bird, D.M. Laudier, R.N. Levy, C.J. Terranova and K.J. Jepsen. Leni and Peter W. May Department of Orthopaedics, Mount Sinai School of Medicine, New York, NY.

Recent literature has shown ambiguity regarding bone mineral density (BMD) scans, the current standard to assess bone fragility. BMD, because it is a complex measure, does not provide insight into the biological mechanisms involved in age-related bone loss and changes in microarchitecture. The goal of this study was to investigate the progression of bone loss in the femur, as part of a global study of the entire skeleton. Non-decalcified, plastic-embedded transverse sections were prepared from nineteen human femurs at 30% and 50% of the length from the proximal end. Each section was imaged using a high-resolution digital camera (10 micrometers/pixel), and measures of bone loss were obtained using image analysis software. These measures included marrow area (MA) and intracortical porosity (ICP) normalized by total area (TA). The ratio MA/TA has been shown to be nearly constant (~0.20) early in life, independent of sex and stature. Age-related changes in the ratios MA/TA and ICP/TA thus reflect endosteal expansion and cortical bone loss, respectively. Endosteal area (MA/TA) increased in a uniform manner ($slope=1.12+0.18$, $p<0.02$) as a function of age and this was similar at the 30% and 50% sites. However, the age-related increase in intracortical resorption (ICP/TA) was twice as great at the 50% site compared to the 30% site. The ratio (MA+ICP)/TA increased with age at both sites. The majority (85%) of this bone loss was due to MA expansion. This data provided important insight into the timing and magnitude of femoral bone loss. Collaborative research involving matched radii found a nearly identical pattern of bone loss, suggesting that the mechanism of bone loss occurs systemically, a finding that has not been equivocally found using BMD.

Role of KLF6 in Liver Development. X. Zhao, N. Matsumoto, and S.L. Friedman. Liver Diseases, Mount Sinai School of Medicine, New York, NY.

KLF6 is a ubiquitously expressed tumor suppressor inactivated in several cancers. KLF6 knockout mice die by fetal day E12.5, with poor formation of blood vessels and no discernible liver. In parallel, ES stem cells lacking KLF6 have been examined for their capacity to differentiate along tissue-specific lineages. The aim of our project was to explore the role of KLF6 in liver development. Although KLF6 is expressed throughout the period of differentiation, we hypothesized that KLF6 expression during a specific time period is enough to ensure proper hepatic differentiation. We assessed the ability of KLF6 -/- embryonic stem (ES) cells to develop into hepatic endoderm. While wild-type ES cells can be driven towards an hepatic lineage under defined culture conditions (Kubo A, et al., Differentiation 2004; 131:1651–1662), KLF6 -/- ES cells minimally differentiate into endoderm precursor cells, expressing only the early hepatic marker gene AFP but not later liver-specific genes such as albumin and TTR. This data suggests that KLF6 is not required for early hepatic development, but is required for more complete differentiation. We also examined KLF6 mRNA in wild-type and KLF6 +/- mice after partial hepatectomy. While KLF6 is induced in both wild-type and heterozygous mice after hepatectomy, its expression level is 50% lower in the heterozygotes. We will next examine whether reduced expression of KLF6 delays or abrogates liver regeneration in heterozygous mice. These experiments provide insights into liver development, which may clarify the basis for liver regeneration, and possibly lead to innovative treatments for patients with liver disease.

Errata

“Ethical Differences Between Socialized and HMO Systems,” Guest Editors: Martin H. Savitz and Michael M. Rivlin. Mt Sinai J Med 2004; 71(6):392–400. Page 394, col. 1, para. 2 should read:

> The Trust and Health Authorities have to live within their budgets and are not permitted to overspend. By the government not providing any extra funds to support the recommendations made by NICE, the result is that lifeboats are being moved around the deck, rather than any extra lifeboats being provided.

Page 400, col. 2, para. 1 should read:

> A general practitioner I had discussed the case with said that he would have accepted the donation....

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06/2004

In Memoriam

Joyce Shriver, Ph.D.

Joyce Shriver, Ph.D., died on October 27, 2004, at the age of 67, after a long illness. She is survived by two brothers, Victor Shriver, Jr., and Gene Shriver, and one sister, Carol Carlberg. A memorial service was held at the Fifth Avenue Presbyterian Church on December 5, 2004.

After receiving her Ph.D. in anatomy from the University of Kansas and completing her postdoctoral training in neuroanatomy at the Columbia College of Physicians and Surgeons, Joyce joined the faculty of the Mount Sinai School of Medicine in 1968, at approximately the same time the school enrolled its first students. Over the years, Joyce was praised by her students for her uncommon commitment and concern and honored with several awards for excellence in teaching. Her legendary courses in neuroanatomy were among the most rigorously and comprehensively taught in the basic science curriculum. In recent years, Joyce developed an outstanding series of neuroanatomy slides to make this difficult subject easier to master.

In addition to her distinguished teaching service, Joyce excelled in the role of Associate Dean for Student Affairs, taking primary responsibility for medical students in their basic science years. In her twenty-five-year administrative tenure, she worked tirelessly to improve the educational experience of Mount Sinai's medical students.

Joyce demonstrated her commitment to both teaching and counseling by developing special—and sometimes unique—programs. With Dr. Hillel Swiller, she developed a student well-being curriculum, which was cited by the American Medical Student Association when presenting its first national Excellence in Medical Education Award to the school. She also assisted in the development of the Cultural Diversity in Medicine program, an elective designed to enhance the cultural awareness of students providing patient care.

Among the other programs under Joyce's direction were an annual book award ceremony, the Patricia Levinson Summer Fellowship Program and a monthly pre-clinical course director's meeting designed to enhance the quality of education in the pre-clinical years. She served on numerous committees, including some of the more challenging ones in the school, such as the Promotions Committee, the Harassment Committee, and the Student Health Committee.

Adventurous and well rounded, Joyce was an active member of several local organizations outside of Mount Sinai, serving on the boards of directors of the Morningside Garden Club and the Jean Cocteau Repertory.

A tribute by the Mount Sinai Alumni Association remembered Joyce as "a thoughtful, empathetic dean and teacher who truly understood the struggles of the young physicians she taught and advised.... Her wisdom, judgment, generous spirit, and constant presence were an inspiration to all who knew her. Having served the School with unwavering loyalty and devotion for thirty-five years, she leaves a legacy of excellence and caring that her colleagues, students, and friends will always treasure."

Committed to the very highest academic standards, Joyce was an exceptionally strong student advocate and a brilliant teacher whose influence remains palpable. In mourning her passing, the Mount Sinai School of Medicine community recognizes her singular contributions to its curriculum and student life.

Barry Stimmel, M.D.
Katherine and Clifford Goldsmith Professor of Medicine
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Endothelial Dysfunction and Antioxidants

W. Lane Duvall, M.D.

Abstract

The vascular endothelium plays a crucial role in the physiology of blood vessels and the pathological processes of atherosclerotic disease and acute coronary syndromes. Endothelial dysfunction is the core problem; it is an impairment of endothelium-dependent vasorelaxation caused by a loss of nitric oxide activity in the vessel wall, which results in impairment in the regulation of vascular homeostasis. Further understanding of its mechanisms of action and possible therapeutic targets will be of great importance. The group of antioxidant vitamins, A, C and E, would seem uniquely situated to reduce cardiovascular events by improving endothelial function by reducing the concentration of reactive oxygen species in the vessel wall and by preventing oxidative modification of low-density lipoprotein. Unfortunately, despite extensive studies in both observational and randomized trials, the weight of evidence points to little or no benefit from antioxidant therapy.

Key Words: Endothelium dysfunction, endothelium, antioxidants, vitamins.

Introduction

Far from being an inert lining, the endothelium is actively involved in a wide variety of physiological and pathological processes. Endothelial dysfunction is an impairment of endothelium-dependent vasorelaxation caused by a loss of nitric oxide (NO) activity in the vessel wall, which results in impairment in the regulation of vascular homeostasis. This impairment can lead to the development of atherosclerosis and the aggravation of myocardial ischemia in the setting of pre-existing coronary disease. One of the proposed mechanisms for endothelial dysfunction involves accelerated NO degradation by reactive oxygen species (ROS) that are created as a byproduct of cellular metabolism. Reducing the concentration of ROS through the use of antioxidant therapy is a potential mechanism for treating endothelial dysfunction. The group of antioxidant vitamins, A, C, and E, are therefore uniquely situated to potentially reduce cardiovascular events by improving endothelial function and also by preventing oxidative modification of low-density lipoprotein (LDL) into the atherogenic oxidized-LDL.

Endothelial Dysfunction

Until recently, the vascular endothelium was considered an inert lining of the blood vessel separating the vascular space from tissues. However, it is now known that the endothelium is actively involved in a wide variety of physiological and pathological processes that mediate inflammation within the vascular wall, plaque stability, thrombus formation, and vasomotor tone (1). The early experiments by Furchgott and Zawadski demonstrated the essential role of the endothelium in reg-

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Instructor of Medicine, the Zena and Michael Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to W. Lane Duvall, M.D., The Zena and Michael Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; e-mail: william.duvall@msnyuhealth.org

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ulating vasodilatation via the endothelial-derived relaxing factor, which was later identified to be NO (2). The endothelium is a single-celled lining covering the internal surface of blood vessels, giving it a strategic location to sense changes in hemodynamic forces and blood-borne signals and respond to them by releasing vasoactive substances. The endothelium thereby plays a key role in maintaining vascular homeostasis by balancing endothelial-derived relaxing and contracting factors.

The term "endothelial dysfunction" has been used to refer to a number of pathological conditions involving the vascular endothelium, for example, altered anticoagulant, antithrombotic and anti-inflammatory properties of the endothelium; impaired modulation of vascular growth; and dysregulation of vascular remodeling (3). Much of the current literature now uses this term to refer to an impairment of endothelium-dependent vasorelaxation caused by a loss of NO activity in the vessel wall. Clinical studies have shown that traditional risk factors for atherosclerosis predispose to endothelial dysfunction (4) and that impaired endothelium-dependent vasodilatation in the coronary circulation predicts adverse cardiovascular events and adverse long-term outcome (5). This decline in NO bioavailability may be caused by a number of different mechanisms: decreased expression of the endothelial cell NO synthase (eNOS), a lack of substrate or co-factors for eNOS, alterations of cellular signaling such that eNOS is not appropriately activated, and accelerated NO degradation by ROS (3).

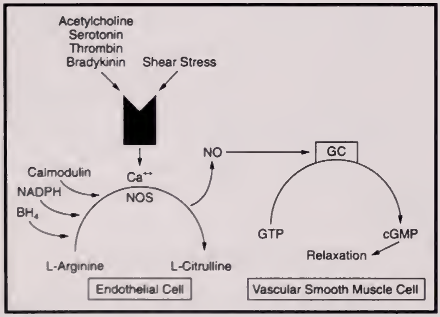

Fig. 1 The nitric oxide pathway. Reproduced with permission from Kinlay S, Ganz P. Role of endothelial dysfunction in coronary artery disease and implications for therapy. Am J Cardiol 1997; 80(9A):11I–16I (1).

BH_4 = tetrahydrobiopterin, Ca++ = calcium ion; cGMP = cyclic guanosine monophosphate, GC = guanylate cyclase, GTP = guanosine triphosphate, NADPH = nicotinamide-adenine dinucleotide phosphate, NO = nitric oxide, NOS = nitric oxide synthase.

NO is the key endothelial-derived relaxing factor that plays a pivotal role in vascular tone and reactivity (6). NO is generated in the endothelial cell by nitric oxide synthase, which converts the amino acid L-arginine to nitric oxide and L-citrulline (Fig. 1). NO diffuses from the endothelial cell to the vascular smooth muscle and increases cyclic guanosine monophosphate, thereby causing relaxation of smooth muscle and dilation of the artery. Luminal diffusion of NO and its uptake into circulating platelets inhibits platelet adhesion and, to a lesser extent, suppresses platelet aggregation. NO can also influence gene transcription, leading to differential expression of cell surface adhesion molecules that influence leukocyte activation, adhesion, and migration.

The endothelium also performs a number of additional functions (7). It further controls vascular tone by secreting prostacyclin, another potent vasodilator, and also secretes the potent vasoconstrictor peptide ET-1 (endothelin-1). It affects coagulation through the secretion of tissue-type plasminogen activator. And it regulates endothelial permeability to lipoproteins and other plasma constituents.

The traditional risk factors for coronary artery disease (CAD), hyperlipidemia, smoking, diabetes and hypertension, are also associated with coronary endothelium dysfunction (8). In fact, the total number of coronary risk factors is related to the reduction in endothelium-dependent vasodilator function (8). It is hypothesized that endothelial dysfunction may initiate the formation of atherosclerotic plaques (9). Atherosclerotic plaques typically form at arterial bifurcations and other sites of disturbed blood flow, and the endothelium is uniquely situated to sense these flow disturbances at the interface of the arterial wall and circulating blood. If dysfunctional, the endothelium potentiates flow disturbances due to improper vasoreactivity, and even initiates the inflammatory response by secreting proinflammatory cytokines and chemokines. These in turn encourage leukocyte activation, promote leukocyte adhesion molecule expression, and facilitate entry of activated leukocytes and LDL into the subintimal space (9). Furthermore, endothelial dysfunction also permits smooth muscle proliferation to proceed unchecked in the media and subintima. These processes are accelerated by the presence of risk factors, and are central to the more advanced stages of atherosclerosis, which are characterized by inflammation and a vulnerable plaque. Finally, impaired endothelium-dependent vasodilatation in coronary arteries with established atherosclerosis results in paradoxical vasoconstriction, which in turn may result in worsened myocardial ischemia during acute coronary syndromes.

Endothelial dysfunction occurs early in the development of atherosclerosis, even before the formation of plaque (10). Measuring and identifying this dysfunction could possibly lead to an early diagnosis of CAD. Endothelium-dependent vasodilatation can be assessed in the coronary and peripheral circulation and be measured both invasively and noninvasively. Fortunately, measures of endothelial dysfunction assessed by peripheral techniques correlate with measures of coronary endothelial dysfunction (11).

A commonly used invasive method employs quantitative coronary angiography to examine the change in diameter in response to intracoronary doses of acetylcholine (12). In healthy arteries, acetylcholine stimulates the release of NO from the endothelium, causing vasodilatation. However, in patients with endothelial dysfunction, a paradoxical vasoconstriction occurs due to the effect of acetylcholine on vascular smooth muscle. Endothelial function can therefore be assessed by comparing the coronary response to acetylcholine with the coronary response to nitroglycerin. Intracoronary Doppler techniques can also be used to measure coronary blood flow in response to pharmacological or physiological stimuli.

The major noninvasive technique involves brachial artery ultrasound to measure the change in diameter of the vessel in response to an increase in sheer stress (13). Upper arm occlusion for 5 minutes results in reactive hyperemia after the cuff is released, causing an endothelium-dependent, flow-mediated vasodilatation. This response is compared to the response achieved from sublingual nitroglycerin to distinguish endothelium-dependent vasodilatation. Doppler echocardiography, positron emission tomography, magnetic resonance imaging, and impedance plethysmography have all been used, although less commonly, to evaluate endothelial function noninvasively (14).

Currently there are several modalities that have been proven to reduce endothelial dysfunction and increase endothelial NO availability (Table).

Some of the most convincing evidence of our ability to treat endothelial dysfunction comes from the substantial data supporting the notion that LDL cholesterol reduction augments endothelial-dependent vasodilatation (15). Most of the relevant studies have observed improvement in acetylcholine-mediated constriction of epicardial coronary arteries and in microvascular dilation. Although a number of modalities that lower cholesterol have been demonstrated to improve endothelial function, much recent attention has focused on the statin class. There is now convincing evidence that statins exert direct, cholesterol-independent (pleotropic) effects to improve endothelial function (16). Such actions may underlie the early and profound effects of these drugs on cardiovascular morbidity and mortality. Trials have shown that treatment and lipid lowering with statins reduce episodes of myocardial ischemia occurring over a shorter period of time than required to obtain regression of atherosclerosis (17, 18). These improvements are, therefore, likely to represent improvement in endothelial-dependent vasomotor function with resultant improved myocardial perfusion. However, studies with other medications and modalities to lower cholesterol have shown improved endothelial function as well, indicating that cholesterol-lowering alone also has significant effect on endothelial function (19–21). In addition to the benefit for endothelial function, large-scale statin studies such as 4S, CARE, LIPID, and HPS have documented this benefit for reductions in clinical cardiovascular events.

The other class of medications with proven significant effects on endothelial function is the

TABLE

Treatment Associated with Improvement of Endothelial Dysfunction

Acute	**Chronic**
LDL lowering with pheresis	LDL lowering with statins, resins
ACE inhibition	ACE inhibition
Antioxidants (vitamin C and E)	Antioxidants (probucol with lovastatin)
Estrogen	Estrogen
L-arginine, D-arginine	Estrogen + progesterone
Tetrahydrobiopterin	L-arginine
Deferoxamine	Exercise
Glutathione	
Calcium channel blockers	

LDL = low-density lipoproteins, ACE = angiotensin-converting enzyme.

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angiotensin-converting enzyme inhibitors (ACE-I). Experimental data suggest that ACE-I's may improve endothelial function by decreasing levels of angiotensin II, by reducing superoxide generation, and by increasing levels of bradykinin and NO (14). The beneficial effects of ACE-I's have been demonstrated in the coronary and peripheral circulation; this becomes apparent after short-term treatment (22). There are potential differences in tissue specificity and the importance of the bradykinin effect among ACE-I's, which have been evaluated in several studies comparing ACE-I's. In a comparison of quinapril, enalapril, losartan, and amlodipine, only the quinapril group showed early improvement in endothelial function (23), while two other studies of enalapril and lisinopril found no benefit (24, 25). The HOPE study generalizes this benefit of improved endothelial function of ACE-I's to hard clinical end points of reduced major cardiac events.

A great deal of evidence indicates that increased vascular free oxygen levels are the prime underlying mechanism for endothelial dysfunction, and as such the use of antioxidants to improve endothelial function would seem to be a logical inference. Unfortunately, there is no corresponding amount of clinical study data demonstrating the efficacy of antioxidants in this setting. Vitamin C supplementation has been shown to improve endothelium-dependent responses in the forearm circulation of patients with various risk factors of CAD (14). However, in other studies, supplementation with Vitamin E or a combination of antioxidant vitamins did not demonstrate any improvement (26, 27). While superoxide dismutase did not show any benefit, the other novel antioxidants probucol, glutathione and N-acetylcysteine have been shown to improve endothelial function in clinical studies (22).

Estrogen is another compound that has been shown to improve endothelium-dependent vasorelaxation via both NO-dependent and independent mechanisms. Administration of estrogen has been shown to improve coronary and peripheral responses to acetylcholine, which occur as soon as 10 minutes after intravascular administration (14, 22). In addition, longer-term benefits may be mediated by estrogen's modification of the lipid profile by increasing high-density lipoprotein (HDL) and decreasing LDL concentrations. Unfortunately, the long-term cardiovascular benefits of hormone replacement therapy have not been demonstrated in clinical trials. On the contrary, the vast majority of randomized studies have shown a trend towards cardiovascular harm with hormone replacement, making the link from endothelial dysfunction to clinical events less apparent.

Antioxidants

Atherosclerosis is a complex process that involves the deposition of plasma lipoproteins, the proliferation of cellular elements, and an inflammatory response in the artery wall. Atherosclerosis advances through a series of stages, beginning with fatty streak lesions composed of lipid-engorged macrophage foam cells and ultimately ending in a complex plaque consisting of a core of lipid and necrotic debris covered by a fibrous plaque (28). Considerable evidence has been gathered to support the hypothesis that oxidative modification of LDL by free radicals is an important step in the development and progression of atherosclerosis (29). At the center of this hypothesis is LDL cholesterol, which undergoes multiple changes upon oxidation that are thought to be proatherogenic (Fig. 2; 30). This theory is termed the "oxidative modification hypothesis." It is be-

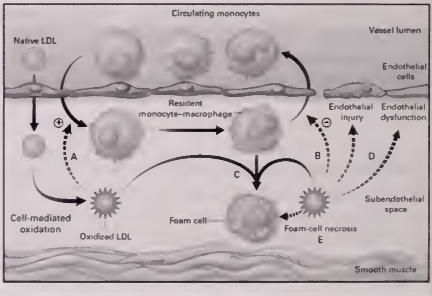

Fig. 2. Early events in atherogenesis. Native LDL becomes trapped in the subendothelial space, where it can be oxidized by resident vascular cells such as smooth-muscle cells, endothelial cells, and macrophages. Oxidized LDL stimulates (plus sign) monocyte chemotaxis (A) and inhibits (minus sign) monocyte egress from the vascular wall (B). Monocytes differentiate into macrophages that internalize oxidized LDL, leading to foam-cell formation (C). Oxidized LDL also causes endothelial dysfunction and injury (D), as well as foam-cell necrosis (E), resulting in the release of lysosomal enzymes and necrotic debris. Broken arrows indicate adverse effects of oxidized LDL. Adapted with permission from Quinn MT, Parthasarathy S, Fong LG, Steinberg D. Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. Proc Natl Acad Sci U S A 1987; 84(9):2995–2998 (30).

LDL = low-density lipoproteins

lieved that unoxidized LDL is not very harmful and is processed by routine lipid metabolism mechanisms without permanent deposition in vessel walls. However, oxidation of LDL leads to the production of a diverse array of biologically active compounds, including some that influence the functional integrity of vascular cells (Fig. 2; 30, 31). Among the most well-characterized effects of LDL oxidation are increases in the expression of endothelial cell surface adhesion molecules that facilitate the mobilization and uptake of circulating inflammatory cells, and alterations in the chemotactic properties of monocytes and macrophages in a manner expected to increase their residency within the artery wall (32). Once the LDL apolipoprotein B proteins are altered by oxidation, they are not recognized by the LDL receptors, but are instead taken up by scavenger receptors. The scavenger receptors are not saturable, and cells with these receptors, namely macrophages, become overloaded with LDL and become foam cells. In addition, oxidative processes are proposed to play a role in lesion maturation and the precipitation of clinical events. This may involve effects on intimal proliferation, fibrosis, calcification, endothelial function and vasoreactivity, plaque rupture, and thrombosis (30).

Oxidants are a chemically diverse group, which are products of normal aerobic metabolism and the inflammatory response. The identification of specific oxidants responsible for disease processes is made difficult by the multitude of pathophysiological events linked to oxidation and the difficulty in measuring the correspondingly short-lived species within the vessel wall. While oxidant formation is inevitable, oxidant-mediated disease is proposed to occur only under circumstances in which these compounds overwhelm antioxidant defenses. Antioxidants also constitute a diverse group of compounds with different properties and mechanisms of action. They can operate by inhibiting oxidant formation, intercepting oxidants once they have formed, or by repairing oxidant-induced injury. With regard to atherosclerotic disease, inhibition of LDL oxidation is the best-characterized effect and includes both reductions in the concentration and reactivity of oxidants, and improved resistance of LDL to these oxidants (30). Steinberg has hypothesized that, unlike agents that lower cholesterol or blood pressure, antioxidants may have to be used for more than five years to have a demonstrable benefit, since the primary mechanism of these agents may be the prevention of new lesions (33). The antioxidants that have received the most attention include vitamin C (ascorbic acid), vitamin E (α-tocopherol), and β-carotene (provitamin A) (32).

Vitamin E

Vitamin E exists as at least 8 naturally occurring compounds, including α-, β-, γ-. and δ-tocopherol and α-, β-, γ-. and δ-tocotrienol, with α-tocopherol being the most active component in natural vitamin E. *In vitro*, vitamin E at high doses blocks the oxidative modification of LDL cholesterol, decreases LDL deposition in arterial walls, reduces monocyte adhesion to endothelium, and inhibits platelet activation (31). These findings, which are in line with the oxidative modification hypothesis, have fueled numerous epidemiological studies and clinical trials on the role of vitamin E in the prevention and treatment of CAD. Unfortunately, although observational trials of vitamin E have been associated with a 20–40% reduction in the risk of coronary disease, randomized trials have not borne out this benefit.

Observational Studies: The US Nurses' Health Study involved approximately 87,000 participants who were followed up for periods of up to 8 years (34). A dietary questionnaire was used to estimate vitamin E intake. Levels of intake were divided into quintiles in women aged 34–59 years who were free of diagnosed CAD, and they were followed for the primary end point of nonfatal myocardial infarction (MI) or coronary death. The study found an adjusted coronary disease relative risk (RR) of 0.66 (95% confidence interval [CI], 0.50–0.87, $p<0.001$) for women consuming the highest vs. lowest amount of vitamin E, after adjustment for age and smoking status. Subsequent analyses revealed a 43% lower risk for vitamin E supplement users vs. nonusers and found that the benefit of vitamin E was only evident after more than 2 years of consumption.

The Health Professions Follow-up Study followed almost 40,000 men aged 40–75 without CAD for up to 4 years, for the occurrence of nonfatal MI, CAD-related death and coronary revascularization (35). Again, the highest quintile of vitamin E consumption was associated with an adjusted RR of 0.64 (95% CI, 0.49–0.83, $p<0.003$). Both studies found that the benefit was primarily evident for those subjects who consumed supplemental sources of vitamin E, and found that cardiovascular protection was maximized at 100 IU/day.

A long-term Finnish study followed 5,000 men and women aged 30–69, free from CAD, for 14 years, for death from CAD (36). An RR of 0.68 (95% CI, 0.42–1.11) for men and 0.35 (95% CI, 0.14–0.88) for women were seen in the tertiles of greatest vs. lowest vitamin E consumption. The tertile boundaries in this study were relatively close, representing only a 25% difference, making the results in this study difficult to interpret.

The Iowa Women's Study, of almost 35,000 postmenopausal women without CAD who filled out questionnaires, was conducted for 7 years and observed for the end point of death from CAD (37). Compared to the lowest quintile of intake, women in the highest quintile had an RR of 0.38 (95% CI, 0.18–0.80, p=0.004). In contrast to both the US Nurses' Health Study and the Health Professions Follow-up Study, this study found benefit only for those subjects who consumed vitamin E in their diet, not in those who used vitamin E supplementation.

The Established Populations for Epidemiologic Studies of the Elderly (EPESE) observed more than 11,000 men and women for 6 years and found that vitamin E supplement use resulted in an RR of 0.53 (95% CI, 0.34–0.84) (38).

There were, however, two negative observational studies for vitamin E. The Scottish Heart Health Study followed almost 12,000 patients for 8 years for the occurrence of new CAD and all-cause mortality (39). No significant benefit was found on the primary end point with higher levels of vitamin E consumption. The Rotterdam Study followed almost 5,000 subjects for 4 years for the occurrence of MI and also found no effect of vitamin E (40).

Randomized, Prospective Studies: The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study randomized more than 29,000 male smokers to 50 IU/day of vitamin E, 20 mg of β-carotene, both, or placebo for 5–8 years (41). While the major end point was lung cancer, major coronary events were a secondary end point. The study found no overall effect on major coronary events for the population as a whole with vitamin E. In the subgroup initially free of CAD, a very modest decrease in the incidence of angina was noted in those taking vitamin E (RR 0.91, 95% CI, 0.83–0.99, p=0.04), while there was no effect on fatal or nonfatal CAD (42, 43). In patients with a history of angina and in those with a history of MI, vitamin E had no effect on any major coronary events (44, 45). One possible confounding factor was that the dose of vitamin E used in this study was lower than the optimal dose of 100 IU/day used in observational studies.

The Cambridge Heart Antioxidant Study (CHAOS) tested the effects of high doses (400 or 800 IU/day) of vitamin E on subsequent cardiovascular events in 2,002 patients with angiographically proven CAD (46). The relative risk of all cardiovascular events was 0.53 (95% CI, 0.34–0.83) for patients who had been taking vitamin E for a mean of 1.4 years. The beneficial effects of supplementation appeared to occur after 200 days of therapy.

The Heart Outcomes Prevention Evaluation (HOPE) Study enrolled 9,541 men and women aged 55 or older who were at high risk of cardiovascular events because they had cardiovascular disease or diabetes with another CAD risk factor (47). Patients were randomized to 400 IU/day of vitamin E or placebo, and followed for a mean of 4.5 years for the primary end point of MI, stroke, or cardiovascular death. The study found no significant differences in the composite primary end point (RR 1.05, 95% CI, 0.95–1.16, p=0.33), in cardiovascular deaths, in MIs, in strokes, or in any of the secondary cardiovascular outcomes.

The GISSI-Prevenzione study randomized more than 11,000 patients surviving a recent MI to either vitamin E (300 mg = 378 IU daily), n-3 polyunsaturated fatty acids, both, or placebo and followed them for 3.5 years for the composite outcome of death, MI, or stroke (48). While the n-3 polyunsaturated fatty acid group showed some benefit, no significant benefit was seen with the vitamin E.

Vitamin A

While vitamin E and vitamin A have been of particular interest because both are carried within LDL particles, β-carotene has less impressive *in-vitro* evidence for preventing oxidative modification of LDL (49, 50). Nonetheless, support for vitamin A has come from many *in-vitro* observational studies that showed cardiovascular benefit in a subgroup of current or former smokers.

Observational Studies: The Health Professions Follow-up Study also accumulated information on β-carotene consumption for the 40,000 men enrolled (35). These men, aged 40–75 and without CAD, were observed for up to 4 years for the occurrence of nonfatal MI, CAD-related death, and coronary revascularization. The highest quintile of vitamin A consumption was associated with an adjusted RR of 0.30 (95% CI, 0.11–0.72) compared to the lowest quintile of consumption. In subgroup analysis, this benefit was only significant for current and former smokers. The Rotterdam Study followed almost 5,000 subjects aged 55–95, without a past history of MI, who filled out dietary questionnaires (40). After 4 years there was a 0.55 relative risk (95% CI, 0.34–0.83, p=0.013) of MI in the highest vs. the lowest tertile of β-carotene consumption. This association was also most evident for current and former smokers.

The Iowa Women's Study followed nearly 35,000 postmenopausal women without CAD who filled out questionnaires on vitamin A consumption (37). After 7 years of observation, there was no significant difference in cardiovascular deaths between the highest and the lowest quintiles of consumption. The Finnish study followed 5,000 men and women without CAD for 14 years, for death from CAD, and no benefit of β-carotene was seen (36). The Scottish Heart Health Study's observation of 12,000 patients for 8 years revealed only a trend towards reducing newly diagnosed CAD and cardiac mortality with higher levels of vitamin A consumption (39).

Randomized, Prospective Studies: The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was designed to determine the effects of antioxidants on the incidence of lung cancer (41). The trial randomized more than 29,000 male smokers to 50 IU/d of vitamin E, 20 mg/d of β-carotene, both, or placebo, and followed them for 5–8 years for the primary end point of lung cancer, with major coronary events as secondary end points. There was no reduction in the risk of lung cancer or ischemic heart disease with β-carotene, and there was an unexpected increase in mortality from lung cancer and ischemic heart disease.

The Beta-Carotene and Retinol Efficacy Trial (CARET) tested the effects of combined treatment with β-carotene (30 mg/d) and retinyl palmitate (vitamin A) in 18,000 patients with a history of cigarette smoking or exposure to asbestos (51). This study, like the ATBC, also showed increases in the risk of lung cancer and ischemic heart disease.

The Physicians' Health Study enrolled 22,000 US male physicians and randomized them to β-carotene (50 mg every other day), aspirin (325 mg/d), both, or neither, and followed them for 12 years (52). No effect was seen with β-carotene on the risk of MI, stroke, or cancer. These results are potentially more robust than the other two trials due to the large sample size, the long duration of observation, and the broader study population, which was not limited to smokers or high-risk individuals.

Vitamin C

Vitamin C is also believed to inhibit oxidative modification of LDL. However, the predominance of evidence does not support the existence of a benefit of vitamin C supplementation.

Observational Studies: The Health Professions Follow-up Study also accumulated information on vitamin C consumption for the 40,000 men enrolled (35). These men without CAD were observed for up to 4 years for the occurrence of nonfatal MI, CAD-related death, and coronary revascularization. There was no effect of vitamin C found on any of the clinical end points. The Iowa Women's Study, of almost 35,000 postmenopausal women without CAD, also found no significant difference in cardiovascular death after 7 years of observation with vitamin C consumption (37). The Established Populations for Epidemiologic Studies of the Elderly (EPESE), which observed more than 11,000 men and women for 6 years, did not find any significant effect on cardiovascular death with vitamin C (38). The Scottish Heart Health Study followed almost 12,000 patients for 8 years for the occurrence of new CAD and all-cause mortality (39). No significant benefit was found, with higher levels of vitamin C consumption, on the primary end point. The Rotterdam Study followed almost 5,000 subjects for 4 years for the occurrence of MI and also found no beneficial effect of vitamin C (40).

The Finnish cohort of 5,000 men and women without CAD were followed for 14 years, for death from CAD (36). The tertiles of greatest vs. lowest vitamin C consumption showed a benefit attributed to vitamin C with an RR of 0.49 (95% CI, 0.32–0.98). The National Health and Nutrition Examination Survey (NHANES 1) followed more than 11,000 men and women for 10 years and found a reduction in cardiovascular death with vitamin C (53). Men with the most vitamin C consumption had an RR of 0.58 (95% CI, 0.53–0.82) and women 0.75 (95% CI, 0.55–0.99).

Randomized, Prospective Studies: The only randomized trial of vitamin C was the Chinese Cancer Prevention Trial, which examined the effect of dietary supplementation on cardiovascular death in almost 30,000 men and women over 5 years (54). One arm of the study involved subjects treated with 120 mg of vitamin C daily, which resulted in no significant effect on cardiovascular death.

Combination Therapy

The use of combination antioxidant therapy has been attempted in several smaller angiographic trials and several large clinical trials.

In a three-year, double-blind trial, 160 patients with CAD, low HDL, and normal LDL were randomized to receive simvastatin plus niacin, antioxidants, both, or placebo (55). The antioxidants consisted of 800 IU of vitamin E, 1000 mg of vitamin C, 25 mg of β-carotene, and 100 μg of selenium daily. The primary end point was change in angiographic stenosis and the occurrence of a first cardiovascular event. Simvastatin plus niacin showed a significant reduction in clinical events and a regression of coronary stenosis compared to placebo; antioxidants were found to have no significant benefit over placebo. In fact, antioxidants in combination with simvastatin and niacin actually attenuated the benefit of the lipid-lowering agents. The frequency of clinical events was 24% with placebo, 21% with antioxidants, 3% with simvastatin plus niacin, and 14% with combination therapy. Coronary stenosis followed a similar trend, with 3.9% progression with placebo, 1.8% with antioxidants, 0.7% with combination, and 0.4% regression with simvastatin plus niacin.

The Women's Angiographic Vitamin and Estrogen (WAVE) Trial randomized 423 postmenopausal women to antioxidants or placebo, and to estrogen or placebo in another arm (56). The antioxidant therapy consisted of 800 IU of vitamin E and 1,000 mg of vitamin C daily. After a mean of 2.8 years, there was a nonsignificant trend towards worsening stenosis in the antioxidant group, with 0.044 mm/year worsening with antioxidants and 0.028 mm/year with placebo.

The Heart Protection Study tested the hypothesis that increased intake of antioxidant vitamins would reduce the risk of vascular disease, cancer, and other adverse outcomes in a UK cohort of almost 21,000 adults 40 – 80 years old (57). These patients, with CAD, diabetes, or other occlusive arterial disease, were randomized to 600 mg (756 IU) vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily or placebo, and followed for 5 years. At the end of follow-up there was no significant difference in all-cause mortality, vascular death, non-vascular death, MI, stroke, or revascularization.

The Chinese Cancer Prevention Trial examined the effect of dietary supplementation on cardiovascular death in almost 30,000 men and women, with 30 IU of vitamin E plus 15 mg of β-carotene daily (54). Patients were followed for 5 years, and no significant effect of antioxidants was seen on cardiovascular death.

Conclusion

At this time the study of endothelial dysfunction and how it relates to the genesis of atherosclerotic disease and the pathogenesis of acute coronary syndrome holds a great deal of promise for improved treatment and prevention of CAD. The vascular endothelium plays a crucial role in the physiology of blood vessels, and further understanding of its mechanisms of action and possible therapeutic targets will be of great importance. Antioxidant vitamin therapy, on the other hand, has already been extensively studied in both large observational and randomized, prospective trials. Unfortunately, the weight of the evidence points to little or no benefit of this therapy in reducing cardiovascular outcomes, and there appears to be no important niche for antioxidant vitamins in cardiovascular therapy.

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Grand Rounds

Restenosis and Drug-Eluting Stents

Robert D. Winslow, M.D., Samin K. Sharma, M.D., and Michael C. Kim, M.D.

Abstract

The implantation of intracoronary stents for the treatment of coronary atherosclerotic disease is one of the most common percutaneous procedures. While the procedure brings long-term benefit for a large percentage of patients, a significant number of patients experience in-stent restenosis (ISR). ISR may be caused by a number of biological and procedural factors, including lesion characteristics as well as co-existing disease states like diabetes. Many strategies have been developed to try to reduce the incidence of ISR. The primary methods include systemic pharmacologic treatments, as well as attempts at modifying stents to reduce their role in the development of ISR. Drug-eluting stents are one such modality, and are expected to become a widely used tool in the field of interventional cardiology. This review will focus on the pathophysiology of ISR and possible ways to prevent it, including drug-eluting stents.

Key Words: Restenosis, drug-eluting stents, review.

Introduction

The treatment of coronary artery disease remains one of the paramount problems in cardiology. In the year 2000, there were 1,025,000 percutaneous transluminal coronary procedures performed in the US, of which 456,000 included the placement of intracoronary stents (1). Stenting is rapidly becoming the preferred method for the percutaneous treatment of coronary artery disease, since it has distinct advantages over angioplasty alone. For example, stents prevent acute vessel closure and early vessel recoil, and improve the long-term patency of vessels. Rates of restenosis in a stented vessel are reported to be as low as 20% and as high as 40%, which is about half that of percutaneous transluminal coronary angioplasty (PTCA) alone (2–5).

One of the major risk factors for restenosis is diabetes, which doubles the incidence when compared to non-diabetic patients (6, 7). Other risk factors include the length of the stented segment and the size of the vessel, with smaller vessels having a higher rate of restenosis (8). There are other characteristics of the vessel itself that contribute to restenosis. Vessels that have undergone remodeling, as defined by intravascular ultrasound (vessel cross-sectional area at the lesion being greater than non-diseased segments), have a higher rate of restenosis, by at least 50%, after both PTCA and stenting (9, 10). There are also poorly understood patient factors that influence both the rate of progression of untreated lesions and restenosis, since patients who get restenosis of treated segments are more likely to have progression of other untreated diseased segments over the same time period (7). Other factors that contribute to the likelihood of restenosis include the amount of damage to the vessel wall during the procedure (11, 12) and the design of the stent itself (13–16).

In-Stent Restenosis

The pathophysiology of in-stent restenosis (ISR) has been well described. It is primarily due to hyperplasia of smooth muscle cells in the intimal layer of the vessel wall (so-called neointimal hyperplasia) and, to a much lesser extent, mural thrombus (17–22). On the molecular and cellular

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From the Zena and Michael A. Wiener Cardiovascular Institute and The Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, NY.

Address all correspondence to Samin K. Sharma, M.D., Cardiovascular Institute, Box 1030, Mount Sinai Medical Center, New York, NY 10029.

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levels, the initial insult is vascular injury caused by both inflation of intracoronary balloons and the metal of the stent itself (23–25). This causes both macrophages and polymorphonuclear neutrophils to migrate to the site of damage, where they release chemokines (19, 21, 26). These chemokines serve to increase the amount of matrix metalloproteinase, which leads to remodeling of the extracellular matrix and smooth muscle cell migration (27, 28). Smooth muscle cells are also stimulated to increase the expression of genes involved in cell division (29). It is both the interaction and the extent of these processes that lead to neointimal hyperplasia and ISR. Compared to restenosis after PTCA, the pathophysiology of ISR may be different. Histologic examination of atherectomy specimens shows a more cellular and proliferative response in ISR than in restenosis after PTCA (30). Stenting also raises the systemic levels of inflammatory markers such as C-reactive protein and interleukin-6 (31).

Efforts to Reduce ISR

Various methods have been employed in the animal lab, as well as the clinical setting and catheterization lab to decrease the incidence of ISR. These methods include systemic administration of drugs, administration of radiation, and coating of stents with a variety of elements, compounds and drugs.

Systemic Administration of Drugs

Some of the first attempts to decrease ISR involved the use of systemic medications that were active against platelet and thrombus formation. While there are some data suggesting that inhibition of thrombus formation decreases neointimal hyperplasia (32), the results in clinical trials using such agents as ticlopidine and aspirin (ISAR trial) (33) and abciximab (ERASER trial) (34) have not shown a decrease in the incidence of ISR. The FLARE trial was designed to test the effects of a statin (fluvastatin) on ISR; it had little effect (35).

One of the more interesting attempts to control ISR is by the administration of systemic glucocorticoids to decrease inflammation and neointimal hyperplasia. A study by Lee et al. randomized patients to a single dose of methylprednisolone prior to stenting. At follow-up angiography, the rates of ISR were 17.5% in the steroid group, vs. 18.8% in the control group (36). The recently published IMPRESS trial took patients with elevated C-reactive protein levels 72 hours after stenting, and randomized them to receive 45 days of prednisone vs. placebo. The group that received prednisone had both a lower event rate as well as lower ISR (7% prednisone, 33% placebo) (37). This evidence suggests that patients with prolonged, active inflammation after stenting derive a benefit from systemic immunosuppression, and that inflammation plays a clinical role in neointimal hyperplasia.

Systemic antiproliferative agents have been studied sparingly in animal models. Everolimus, a macrolide antibiotic similar to rapamycin, was given to rabbits both before stenting and for one month after the procedure to study its effects on ISR. The groups receiving active drug had an approximately 45% reduction in neointimal thickness, but significant systemic side effects, mostly gastrointestinal. Histologic examination of arterial specimens demonstrated more healing of the endothelium and intimal wall than studies using coated stents (38).

While some systemic treatments show promise, early experiences did not demonstrate significant reduction in the rate of ISR. The concentrations of medicines at the site of pathology in the coronary artery may not have been high enough, and the side effects of systemic administration may have limited appropriate dosing. This led to the theory that coating of stents with compounds or medications may allow for local delivery of a substance in a concentration high enough to disrupt the restenotic process.

Principles of Coated Stents

Stents are made primarily from surgical-grade stainless steel. The first generation of coated stents added an element such as carbon or gold to the stent surface to give it different properties. The next generation of coatings consisted of polymers that could be used primarily as reservoirs for other drugs or substances. These matrices enabled the coating to be durable, uniform and able to reliably deliver doses, while controlling the kinetics of delivery. And they enable drugs to elute into the surrounding tissue over time frames of approximately one month (39–41). After the initial studies of these polymer coatings in animals, it was noted that the polymers themselves could increase inflammation and neointimal hyperplasia, compared to bare metal stents (42–44). The biocompatibility of both the matrix and the drug are important in understanding the effects on the vessel wall and ISR after implantation. The coatings themselves are not always stable during expansion and sterilization, which is another factor that contributes to the effects of coated stents (45). Therefore, the coatings must be stable both when applied to a stent and during deployment, the matrix must be biocompatible and not increase ISR by itself, and the medicine must be delivered in the correct concentrations and with the proper kinetics.

The most common drugs applied to coated stents are anticoagulants (heparin), steroids, and antiproliferative agents like paclitaxel and rapamycin (Table 1).

TABLE 1
Substances Examined as Stent Coatings

Coating	Mechanism of Action
Biocompatible	
Gold	Inert and possibly anti-inflammatory
Carbon	Inert and possibly anti-inflammatory
Si Carbide	Inert and possibly less thrombogenic
PC	Organic polymer possibly less thrombogenic
Drug Coatings	
Anticoagulants	
Heparin	Antithrombotic and possible SMC inhibition
Antimitotic agents	
Paclitaxel	Mitotic inhibitor
Sirolimus	Immunosuppressive and SMC inhibition

Si= silicon, PC= phosphorylcholine, SMC= smooth muscle cell

Elemental Coatings

The first element used to coat stents was carbon, under the assumption that it might present a less thrombogenic surface to the artery (46). Initial animal data had shown both safety and a trend towards a decrease in restenosis and neointimal hyperplasia at 6 weeks (47). Nonrandomized human studies using the carbon-coated stent showed a restenosis rate of 11% in intermediate risk patients (47) and of 25% in high-risk patients (48). While not randomized or controlled, these results implied a trend towards a lower rate of ISR than with uncoated stents.

There is extensive experience in coating stents with gold. Gold has long been used as an anti-inflammatory agent in rheumatoid and psoriatic arthritis. Gold is also biocompatible and resists corrosion, and is more radiopaque and easier to see with X-ray cineangiography. Initial studies using gold-coated stents showed equivalency with uncoated stents (49, 50), but there was a suggestion that in high-risk patients, there was a higher incidence of ISR (49, 50). In a randomized trial of gold-coated stents vs. uncoated controls, there was no significant difference in acute or subacute events or in survival, on initial analysis (51). On clinical follow-up, there appeared to be an increase in adverse cardiac events as well as angiographic evidence of more ISR, in the gold-coated stent group (52, 53). When using intravascular ultrasound, neointimal tissue proliferation was detected more often in the patients with gold-coated stents than in those with bare metal stents (53, 54). Because of the discouraging results with gold-coated stents, they are no longer being aggressively pursued as a restenosis cure.

Stents Coated with Biocompatible Materials

Several trials have considered possible reduction in ISR with stents coated with silicon carbide and phosphorylcholine. Silicon carbide is an inert semiconductor that is both biocompatible and hemocompatible (55), and it is less thrombogenic than bare metal (56). The patients in the studies looking at silicon-carbide-coated stents had a limited number of follow-up angiograms, but the rate of ISR seemed to be similar to that with uncoated stents (57).

Phosphorylcholine is a phospholipid that is found in normal cells, and theoretically might be less thrombogenic or result in less neointimal hyperplasia, by presenting the vessel wall with a familiar surface. Animal data, however, suggests that it has little effect on the development of neointimal hyperplasia and ISR (58). Human studies in patients at high risk for ISR did show a lower than expected rate (6 – 17%), but many patients did not have follow-up angiograms, so the true magnitude of this effect is not known (59, 60).

Stents Coated with Anticoagulant Agents

Heparin has long been studied as a coating for metal stents, under the assumption that the heparin coating may decrease the thrombogenicity of the stent and may lead to less neointimal hyperplasia. Animal data supports the decreased thrombogenicity, but has produced conflicting data regarding its effects on ISR (61, 62). Further testing has shown that if multiple layers of heparin are used, there is less neointimal hyperplasia in an animal model of ISR (63). The MENTOR study took patients at low risk for restenosis and implanted heparin-coated stents. These stents had a rate of ISR similar to that of uncoated stents (approximately 22%) (64). Heparin-coated stents have also been studied in acute myocardial infarction, without glycoprotein IIBI-IIA antagonists or heparin as adjunctive therapy. There was no subacute thrombosis, and a 17% rate of ISR (65). The only trial randomizing patients to heparin vs. uncoated stents had a similar rate of restenosis in both arms of the study, of approximately 30% (66). Overall, human data suggest that coating stents with heparin does decrease the rate of subacute thrombosis, but has little effect on ISR.

Stents Coated with Antiproliferative Agents

Paclitaxel

Paclitaxel is a derivative of taxol with antimitotic properties. It inhibits microtubule depolymerization, and therefore arrests the cell cycle and stops proliferation. Initial data from animal studies showed a significant effect on reducing ISR when stents were coated with paclitaxel, with a decrease in the rates from 35% to 5% (67) and a difference in late luminal loss from 51(27% to 27(27% of the vessel diameter (Fig. 1; 68).

There are a number of human studies using paclitaxel-coated stents (Table 2; 69–72). The ASPECT trial randomized 177 patients to bare-metal stents, and both low- and high-dose paclitaxel-coated stents. The results of this dose-finding study showed that the high-dose-coated-stent group had a binary restenosis rate of 4% vs. 27% for the control. The average diameter stenosis was 14% in the high-dose group and 39% in the control group (69). When the drug-coated vs. bare-metal stents were compared in an intravascular ultrasound (IVUS) substudy, the drug-coated stent group had significantly decreased neointimal hyperplasia (73). In ELUTES, 192 patients at low risk for restenosis were randomized to receive paclitaxel-coated stents at 4 different concentrations vs. the control group with bare-metal stents. There was a 3% restenosis rate in the high-dose group and a 21% rate in the control group (70). Not all trials with paclitaxel or its derivatives showed such promising results. The SCORE trial used stents coated with QP-2 (a taxane analogue similar to paclitaxel); the study was ended prematurely because of an increased risk of subacute, in-stent thrombosis. Angiographic data suggested that at 6 months the amount of neointimal proliferation was less, but the study was never completed (74).

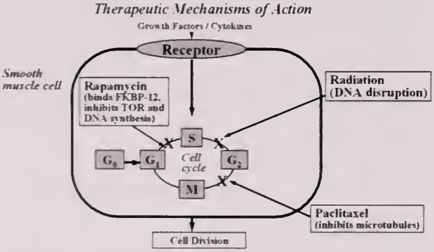

Therapeutic Mechanisms of Action
Growth Factors / Cytokines
Receptor
Smooth muscle cell
Rapamycin (binds FKBP-12, inhibits TOR and DNA synthesis)
Radiation (DNA disruption)
S
G₀
G₁
Cell cycle
G₂
M
Paclitaxel (inhibits microtubules)
Cell Division

Fig. 1. Schematic of smooth muscle cell cycle, and site of action of antiproliferative agents.
FKBP = FK binding protein, TOR = target of rapamycin.
S = synthesis, G_0 = growth phase$_0$, G_1 = growth phase$_1$, G_2 = growth phase$_2$, and M = metaphase.

TAXUS is a series of studies designed to look at the effectiveness of paclitaxel-coated stents on ISR. TAXUS-I randomized 30 patients to receive uncoated stents and 31 to receive paclitaxel-coated stents. The patients were at low risk for restenosis (3–3.5 mm vessels, requiring one stent), as evidenced by the 10% restenosis rate in the uncoated-stent group. The ISR rate in the paclitaxel group was 0%, but this did not achieve statistical significance. One of the only significant results of this study was a diameter stenosis at six months of 13.6±11.8% in the paclitaxel vs. 27.2±16.7% of the control stents (71). In the TAXUS-II trial, which used the same stent as TAXUS-I, 536 patients were randomized into 2 divisions, one of which was further randomized to receive a paclitaxel-coated stent with slow-release kinetics vs. uncoated stents. The other division received moderate-release paclitaxel vs. uncoated stents. All patients received aspirin and clopidogrel. The rates of ISR were approximately 20% in both control groups and 8% in both active drug groups at 6-month follow-up angiography (72). The TAXUS-III trial enrolled 28 patients, who were given up to

TABLE 2
Randomized Trials for Primary Restenosis Using Paclitaxel

Trial	# of Patients	ISR Risk	ISR: Control	Active
ASPECT (69)	177	NR	27%	4%
ELUTES (70)	192	Low	21%	3%
TAXUS I (71)	30	Low	10%	0%*
TAXUS II (72)	536	"Standard"	20%	6%

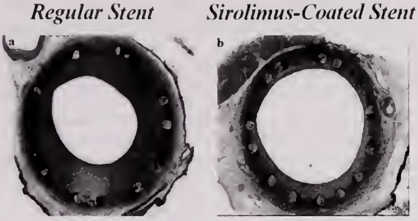
NR= not reported
* p=ns

2 stents for the secondary treatment of ISR, but not for primary prevention. Twenty-five of these patients had follow-up angiography. There was a 16% rate of restenosis (4 of 25), and the loss of luminal diameter was statistically greater in those who received 2 stents (75). TAXUS-IV was a large, prospective trial that compared paclitaxel-coated stents to bare-metal stents in the treatment of de novo coronary stenoses in 1,314 patients. In 559 patients who had angiography at 9 months, restenosis was reduced from 26.6% to 7.9% (76).

Despite promising early results, there is some concern about the long-term outcomes with paclitaxel-coated stents. While decreasing the rate of ISR, histologic analysis of the vessels with paclitaxel-coated stents showed less healing of the vessel wall after stenting. There was chronic low-grade inflammation, poor healing of the endothelium, and intra-intimal hemorrhage (77). In one of the only published 12-month angiographic studies, there was a 60% rate of restenosis seen at follow-up angiography. Although the sample size was small (15 patients), the suggestion is that this antiproliferative agent might only delay the onset of restenosis, or may cause late restenosis through different mechanisms, mainly delayed healing of the endothelium and vessel wall (78).

Rapamycin

Rapamycin (sirolimus) is a macrolide antibiotic that was discovered in a microbe on Easter Island. The molecule possesses antiproliferative effects on smooth muscle cells by inhibiting growth-factor- and cytokine-induced cell division (79), a property that was noted in the early 1990s. The drug is attached to the metal of a stent, with an outer layer of biocompatible polymers that enable the drug to elute over a 30-day period (80). Initial results in animal studies showed a significant decrease (up to 50%) in ISR and amount of inflammation in lesions treated with stents coated with rapamycin (81, 82; Fig. 2).



Courtesy S. Sharma, M.D.

Fig. 2. Restenosis and drug-eluting stents. **(a)** Regular stent: moderate neointimal hyperplasia formation encroaching the lumen of a normal porcine coronary artery. **(b)** Sirolimus-coated stent: significantly less neointimal hyperplasia despite a similar degree of vessel injury.

The FIM (First in Man) study was a nonrandomized study of a rapamycin-coated stent (Table 3; 83–85). A cohort of 30 patients studied had a striking 0% ISR rate on angiography at 4 months (86, 87). Another 15-patient cohort had no ISR, and a 0% loss of diameter by IVUS at 6 months (88). In the composite of these groups, there were no adverse cardiac events over a 12-month clinical follow-up period.

The RAVEL study took 238 patients and randomized 120 to receive a rapamycin-eluting stent and 118 a bare-metal control. They were all treated with clopidogrel or ticlopidine, and only 10% of patients received a glycoprotein IIBIIIA inhibitor. The rate of ISR was 0% in the rapamycin group and 26.6% in the control group (89). The results were validated using IVUS, and the zero restenosis rate was true for some of the higher risk patients, those with small vessels (90) and those with diabetes (83).

The results of the largest trial in rapamycin-eluting stents, the SIRIUS trial, were recently reported. The trial took 1,101 patients with de-novo

TABLE 3

Trials for Primary Restenosis Using Rapamycin

Trial	# of Patients	ISR Risk	ISR: Control	Active
FIM (83)	45	NR	N/A	0%
RAVEL (84)	238	Moderate	27%	0%
SIRIUS (85)	1101	Moderate	35%	3%
diabetes subgroup	279	High	49%	8%

NR = not reported, N/A = not applicable

FIM = First in Man; RAVEL = RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions; SIRIUS = SIRolImUS-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions.

coronary lesions and randomized them to receive rapamycin-coated stents (556 patients) or uncoated controls (545 patients), of which 533 received coated stents and 525 bare metal stents. The rate of ISR was 35% in the control group vs. 3% in the rapamycin group at 8 months. There was a slightly higher rate of restenosis in the area immediately outside the stented segment in an additional 6%. The results were even more striking in diabetics, with an ISR rate of 49% in controls and 8% with rapamycin (85).

Rapamycin-eluting stents have also been applied to the treatment of ISR. A study by Degertekin et al. took 16 patients with ISR of 2.5 – 3.5 mm vessels; 4 patients had had previous brachytherapy for ISR. A total of 26 stents were placed. There was one sudden death, one late stent occlusion, and 3 instances of ISR in the 16 patients (84). These results compare favorably with those obtained with radiation therapy. However, further studies in the use of drug-eluting stents to treat ISR are needed.

Intracoronary Radiation Therapy

Intracoronary radiation therapy, or brachytherapy, has been studied primarily for treatment of ISR. The initial experiences were hampered by both the need for a high dose of radiation and a high rate of edge restenosis ("candy-wrapper" effect). After these problems were addressed, many studies using various forms of radiation have shown a benefit in secondary prevention of ISR. The SCRIPPS, GAMMA-1 and WRIST trials, using gamma radiation, and PREVENT, using beta radiation, significantly decreased secondary ISR (85, 92 – 94). The control patients who underwent PTCA of the segment had a 50 – 60% rate of restenosis, while those patients who underwent PTCA and radiation therapy had a 17 – 32% rate, thus preventing restenosis in an additional 50 – 60% of cases after treatment for ISR. When the procedure consists of rotational atherectomy and radiation treatment, a 10% rate of ISR has been reported (95). Interestingly, longer follow-up angiography on patients treated with radiation shows that after a significant decrease in restenosis at 6 months, there is progressive narrowing over the next 3 months, with an additional 20% of patients meeting criteria for ISR by the 12-month mark (96).

Discussion

The factors that influence vessel patency after a percutaneous procedure are numerous and complex. There are a number of biological factors: coexisting diabetes, vessel size and prior remodeling. Characteristics of the procedure also play a significant role, including the amount of damage to the vessel wall, ostial lesions, and the type of stent used. Coating of stents adds additional problems: the material itself and its biocompatibility, as well as the choice of drug, its pharmacologic effects and the pharmacokinetics of its delivery. Stenting itself reduces the rate of restenosis in percutaneous procedures, but because the overall rate of primary ISR remains near 20%, there is great interest in how to decrease it. The most promising results so far have been seen with stents coated with antiproliferative compounds, with a decrease in the rate of ISR of approximately another 50 – 60%. Yet there is a lack of long-term follow-up, and it is possible that these agents may only delay the phenomenon, not prevent it entirely.

Other treatments show promise, as the ability to modify multiple aspects of the restenotic cascade are mapped out. For example, anti-inflammatory agents, including steroids, may help to decrease primary ISR, without specifically attacking smooth muscle cell proliferation.

The treatment of ISR poses a problem for cardiologists. Most randomized trials show that the mechanical treatment of ISR results in a 50 – 60% rate of secondary stenosis. Primary biologic factors are the most likely reason that patients who have ISR are at the highest risk to restenose. Neither the coating of stents with antiproliferative agents nor the addition of brachytherapy has been able to eradicate the problem of secondary stenosis.

Drug-eluting stents coated with antiproliferative agents seem to be able to prevent early ISR in the vast majority of patients who are predisposed to its development. Thus, they will probably be widely used. Nonetheless, more long-term follow-up studies are needed to determine whether this strategy actually prevents or merely delays the process. Some patients may need additional therapeutic strategies to eliminate the problem.

Drug-eluting stents also add a significant cost to the stenting procedure, with a drug-eluting stent costing approximately an extra $2,000 (97). Restenosis impacts the cost of percutaneous interventions as well. It is estimated that the treatment of ISR costs $8,000 – $28,000 per episode, which adds $1,500 – $8,000 for each patient who receives a stent, regardless of whether they develop ISR (98). It seems economically viable to use drug-eluting stents for patients who need stenting, especially if only one stent is used and the patients' risk of restenosis is high.

Because of cost issues, not all patients will be able to receive drug-eluting stents. Further research is needed to determine which subgroups will benefit most. Perhaps a formal recommendation from a national agency such as the American Heart Association or the American College of Cardiology will be of help.

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New Trends in Lipid Management:

Eight Cases to Consider

Donald A. Smith, M.D., M.P.H.

Abstract

Eight case histories with differing clinical presentations and lipid abnormalities are presented to illustrate new trends in lipid management. Issues discussed include the use of coronary artery calcium scores to assess coronary heart disease risk for individuals who are asymptomatic, lower LDL-cholesterol goals, new lipid measurements that may be clinically helpful in patient management, and the use of combined lipid-altering agents.

Key Words: Anticholesterolemic drugs, coronary disease, lipids, drug therapy, cardiovascular diseases, lipoproteins, cholesterol, triglycerides, drug therapy, mortality, prevention, control.

In the 1990s, at the Mount Sinai Cardiology Clinic and Cardiology Faculty Practice, only 5% of patients with proven coronary heart disease were on two or more lipid-altering medications (1). Since that time, several provocative studies have been published which suggest that low-density-lipoprotein cholesterol (LDL-C) guidelines should perhaps be more demanding for patients with coronary heart disease (CHD) (2–4) and that combination therapy with two different classes of lipid-altering agents may produce more beneficial clinical outcomes than might be expected from studies using only a single agent (5).

In 2001 the Adult Treatment Panel III (NCEP ATP III) of the National Cholesterol Education Program (NCEP) (6) suggested the possible utility of measuring nontraditional CHD risk factors such as ultrasensitive C-reactive protein and lipoprotein (a) (Lp(a)) to help better estimate CHD risk for those patients without a history of CHD. In addition, they proposed that surrogate measures of atherosclerosis, such as intima-media thickness of the carotid artery, ankle brachial index, and ultrafast or multi-detector computer tomographic (UFCT) scanning of coronary arteries for coronary calcium scores, could also be performed for sharpening CHD risk estimates. LDL-C goals were lowered to less than 100 mg/dL for those with diabetes and for those with a CHD risk equivalent, i.e., more than a 20% 10-year-risk of a myocardial infarction (MI) or CHD death as determined by a Framingham risk algorithm. Non-high-density-lipoprotein cholesterol (non-HDL-C) goals were recommended for those with triglycerides over 200 mg/dL, to estimate all atherogenic apolipoprotein B (Apo B) lipoproteins in one number. Triglyceride goals were set optimally as less than 150 mg/dL.

More recently another paper from the Coordinating Committee of the NCEP (7) has recommended an LDL-cholesterol goal of < 70 mg/dL as a therapeutic option, based on clinical trial evidence in those persons at *very high risk*. Such persons include those with established cardiovascular disease and a recent acute coronary syndrome, or multiple risk factors (especially diabetes), or severe and poorly controlled risk factors such as continued cigarette smoking, or multiple risk factors

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Department of Medicine and Community and Preventive Medicine and Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Mount Sinai Medical Center, New York, NY.

Address all correspondence to Donald A. Smith, M.D., M.P.H., Box 1014, Mount Sinai Medical Center, 1 East 100th Street, New York, NY 10029-6574.

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of the metabolic syndrome (especially triglycerides ≥ 200 mg/dL plus non-HDL-cholesterol ≥ 130 mg/dL with low HDL-cholesterol < 40 mg/dL). This report also suggested as a therapeutic option a primary-prevention LDL-cholesterol goal of < 100 mg/dL in persons with an LDL-cholesterol > 100 mg/dL and a moderate 10-year risk of 10–20% with several other risk factors such as hypertension, advancing age, continued smoking, a strongly positive family history of premature atherosclerotic cardiovascular disease, lipids consistent with the metabolic syndrome as stated above, or with a C-reactive protein > 3 mg/L, or a coronary calcium score > 75th percentile for a person's age and sex. This recommendation was based on evidence from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (8), in which the use of 10 mg of atorvastatin for 3.3 years reduced the risk of MI and CHD death by 36% and stroke by 27% in the 10,300 participants age 40 to 79 years without coronary heart disease but with hypertension and 3 other risk factors. The report emphasizes that a standard dose of a statin be used to reduce the LDL-cholesterol by at least 30–40% and minimally to a level <100 mg/dL.

It takes some time for more aggressive guidelines to be implemented, and studies showing the inability of physicians to obtain guideline lipid goals have been discouraging (9). But change does occur. For example, the percentage of patients with CHD who had LDL-C of less than 100 mg/dL increased from 23% to 53% between 1994 and 1999 at the Mount Sinai Cardiology Clinic and Cardiology Faculty Practice (10). The same results will surely occur elsewhere as the clinical evidence for more aggressive lipid-altering therapy mounts. This article will present cases to illustrate several clinical points that may be helpful to the practicing physician in assessing CHD risk and preventing cardiovascular events through the treatment of atherogenic lipids.

A. Be suspicious of patients with family histories of early CHD: Consider using non-invasive imaging studies to assess individual risk in order to lower atherogenic lipids sufficiently.

Case 1: 52-Year-Old Male (Fig. 1)

How many CHD risk factors are there? What is the LDL-C goal? In order to determine an LDL-C goal, one first establishes that the patient has 3 of 5 potential CHD risk factors used in the ATP-III algorithm:

- Age: over 45 in males, over 55 in females
- Positive family history (FH) of CHD: < 55 years old in first-degree male, < 65 years old in first-degree female
- HDL-C < 40 mg/dL

Case 1 52-year-old male

Negative history of CVD, DM, HTN, and smoking.

Father MI at 63, brother MI at 47.

HT: 5'7" WT: 158lbs IW: 145lbs
BP: 104/82

Lipid profile (mg/dL)

TC	TG	LDL-C	HDL-C	T/HDL-C ratio
232	152	37	165	6.3

Fig. 1. Case 1: 52-year-old male
BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HT = height; HTN = hypertension; IW = ideal weight; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TC = total cholesterol; TG = triglycerides; WT = weight; T/HDL ration = TC divided by HDL-C.

His NCEP ATP-III LDL-C goal is thus < 130 mg/dL.

The patient then began what was supposed to be a 2-month trial of dietary therapy, which involved lowering animal saturated fats and trans fatty acids, and consuming soluble fiber and stanol ester margarines. This could have lowered his LDL-C by 10–15%. He only returned 2 years later because a brother had suffered a heart attack at a family reunion. He panicked and was afraid to move quickly for fear of precipitating a heart attack. While waiting to get a stress test, he obtained an electron-beam computed tomography (EBCT) coronary artery calcium score (CACS) and repeated his lipids levels. The following were the results (Fig. 2).

Given his EBCT coronary artery calcium score and Bruce stress echocardiographic results, what now is his LDL-C goal? How can it be accomplished?

The use of electron beam or multi-detector CT scanning for coronary artery calcium scoring has become one method of assessing CHD risk for patients with no history of clinical CHD (11). This patient's high coronary artery calcium score (CACS) would predict a substantially increased risk of nonfatal MI or CHD death over the next 8.5 years (12). In fact, it would push him into a CHD risk equivalent state. Thus, although he had no symptomatic CHD, my goal for his LDL-C was lowered to less than 100 mg/dL, a 40% decrease in his current LDL-C level, a therapeutic option now suggested by the NCEP committee (7). This goal could most probably be achieved with rosuvastatin 10 mg qd, atorvastatin 20 mg qd, or simvastatin 40–80 mg qd (13).

Case 1 52-year-old male 2 years later

Brother 53 sudden MI at family reunion.
Onset atypical chest pain.
Fears any movement.

Lipid profile (mg/dL)

TC	TG	HDL-C	LDL-C	T/HDL ratio
227	140	32	167	7.1

EBCT: Agatston Score = 1140,
> 90th percentile for age, gender.
Bruce stress echo: Peak HR 155, SBP 120 to 170, no ECG changes. LV wall motion normal with diffuse hyperdynamic changes and increase in EF. No evidence of ischemia.

Fig. 2. Case 1: 52-year-old male 2 years later
EBCT = electron-beam computed tomography; ECG = electrocardiogram; EF = ejection faction; HR = heart rate; LV = left ventricle; SBP = systolic blood pressure.
For all other abbreviations, see Fig. 1.

The question that remains in terms of lipid altering for this man with asymptomatic coronary vascular disease, or for someone with symptomatic or documented obstructive coronary heart disease, is how low to push LDL-C levels. Although many LDL-C lowering trials can show primary or secondary prevention effects of 25–35% in CHD event rates, this still leaves a substantial number of persons with CHD events (2, 14–17). One trial, to be reported in the spring of 2005, may help answer this question. Treating to New Targets (TNT) is a randomized, double-blind study funded by Pfizer, assigning 10,000 participants with known CHD to 10 vs. 80 mg of atorvastatin (18). To qualify, a participant must have been able to lower LDL-C to 100–130 mg/dL with atorvastatin 10 mg per day. Participants were then randomized to remain on atorvastatin 10 mg or to increase to 80 mg qd to attain an LDL-C level in the 50–80 mg/dL range. The hypothesized result would be an improvement in event rate reduction on the higher dose with the lower LDL-C levels. Results from a similar secondary prevention trial, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) (19), comparing simvastatin 20 vs. 80 mg qd for 12,000 participants, should be available by 2006.

A recent intravascular ultrasound trial has been somewhat enlightening in regard to the matter of target LDL-C for patients with CHD. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL), recruited 654 patients with symptomatic CHD, and at least one coronary vessel with > 20% stenosis and LDL-C baseline values of 125–210 mg/dL, and randomized them to pravastatin 40 mg or atorvastatin 80 mg for 18 months (3). LDL-C levels were reduced to 110 mg/dL or 79 mg/dL, respectively. Intravenous ultrasound studies to evaluate atherosclerotic plaques in 30 mm segments of coronary arteries with 20–50% stenoses demonstrated that patients on atorvastatin had no increase in atheroma volume (–0.4%) compared with an increase in those on pravastatin (+2.7 %, p=0.02 between the two groups). This would suggest that an LDL-C of 80 mg/dL or lower would be required for those persons not wishing coronary plaque growth.

Such a clinical difference in cardiovascular (CV) events for patients using the same medications and dosages was recently published by the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) group (4). This study enrolled 4,162 patients hospitalized with acute coronary syndromes and randomly assigned pravastatin 40 mg vs. atorvastatin 80 mg. After a follow-up period of 18–36 months (mean 24 months), patients on atorvastatin compared with those on pravastatin had a 16% reduction in the primary end point of all-cause death, MI, unstable angina requiring rehospitalization, revascularization and stroke (26.3% vs. 22.4% respectively, p=0.005). Trial LDL-C values were 95 and 62 mg/dL, respectively. This study pertains only to the approximately one million persons who have MIs and unstable angina in this country annually, and there were some subgroups whose results were not significantly different for patients on the two drugs (those ≥ 65 years, with MI with ST-segment elevation, previously on a statin, and with LDL-C < 125 mg/dL). Whether equivalent levels of LDL-C will be associated with similar decreases in coronary event rates in the much larger part of the population with a history of stable CHD awaits the larger TNT and SEARCH clinical trials mentioned above, with thousands of patients. My LDL-C goal for this man at this point would certainly be < 100 mg/dL, and preferably < 70 mg/dL.

Case 2: 66-Year-Old Woman (Fig. 3)

How should she be treated?

It was unclear whether this patient's LDL-C of 209 mg/dL was atherogenic, given her high HDL-C of 70, which produced a TC/HDL-C ratio of 4.2 (near the ideal range of < 4.0). Her only NCEP ATP III risk factor was age (> 65 years in women), which was offset by her high HDL-C level. Thus, with zero risk factors in the NCEP ATP III algorithm for determining coronary disease risk, her LDL-C goal was < 160 mg/dL. The history of a heart condition in a brother of approximately the same age, however, sent a warning signal that demanded further attention to her CHD risk. The

Case 2 66-year-old woman

Brother with "heart condition."
Neg history of DM, HTN, smoking
On hormone replacement therapy x 10yrs
Atorvastatin 20mg - AST 70 U/L / ALT 103 U/L

PE: 5'2" WT: 126 lbs IW: 120 lbs
BP: 136/75

Lipid profile (mg/dL)

TC	TG	HDL-C	LDL-C	T/HDL-C ratio
292	65	70	209	4.2

EBCT coronary calcium score 334 Agatston units, 90th percentile for age, gender

Fig. 3. Case 2: 66-year-old woman
ALT = alanine aminotransferase (normal≤ 60 U/L); AST = aspartate aminotransferase (normal ≤ 50 U/L).
For all other abbreviations, see Figs. 1 and 2.

Case 3 53-year-old female

Hypercholesterolemia for years.
Negative exercise stress test
HTN, on angiotensin II receptor blocker and diuretic.
While on simvastatin (Zocor) or atorvastatin (Lipitor): experienced aches so each was discontinued

FH: Brother MI at age 87

HT: 5' 3" WT: 208 ibs IW: 135 lbs BP: 164/90, 145/88 mm Hg

TC	TG	HDL	LDL	T/HDL	
326	60	65	249	5.0	Atorva 10 mg
514	70	72	428	7.1	Fluvastatin XL 80 mg
314	76	72	227	4.4	Ezetimibe 10mg
244	47	75	160	3.3	

Fig. 4. Case 3: 53-year-old female
Atorva = atorvastatin (Lipitor), Ezetimibe (Zetia).
For all other abbreviations, see Fig. 1.

EBCT score at the 90th percentile for a woman her age suggested that the HDL-C was in fact not that helpful and certainly did not override the unknown family history risk. Given the high coronary calcium score, her LDL-C goal decreased from < 160 mg/dL to < 100 mg/dL and justified the effort to search for lipid-altering medications that would lower LDL-C to that level without giving the abnormal liver function tests (LFT) produced by atorvastatin 20 mg qd. Alternatives included a lower dose of atorvastatin or rosuvastatin, combined with a bile acid binder or a cholesterol receptor inhibitor, as illustrated in the following cases.

B. Combine therapies to reduce LDL-cholesterol further into the good range.

Case 3: 53-Year-Old Postmenopausal Female (Fig. 4)

This patient's only ATP III CV risk factor is hypertension, which is offset by a negative risk factor of having high high-density lipoprotein cholesterol (HDL-C), which was > 60 mg/dL. Thus, by NCEP ATP III criteria, her LDL-C goal is < 160 mg/dL. To reduce LDL-C from 428 to 160 mg/dL in a patient with familial heterozygous hypercholesterolemia, would almost certainly require, at a minimum, the use of a statin. Although the original fluvastatin preparation, even at 80 mg per day, had the least potency of all the statins, its reformulation into a gel matrix form, fluvastatin XL 80 (Lescol XL 80), has increased its ability to lower mean LDL-C by 37%. By combining fluvastatin with hydrophilic polymers which absorb water on ingestion and form a gelatinous outer coat, the gastrointestinal absorption of fluvastatin is extended to more than 8 hours, causing a lower maximum serum peak level after administration compared to other statins. A report of the pooled clinical trial data using fluvastatin 20, 40, and XL 80 showed a low and equivalent (< 1%) percentage of people of all ages with creatine phosphokinase (CPK) elevations greater than 5 times the upper limit of normal compared to placebo (20). This may validate fluvastatin as a statin that can be tried in patients who have myalgias as a result of usage of other statins. Although other studies have essentially reported no differences in CPK elevations among all the statins (21), our "case 3" patient was started on fluvastatin XL 80, with a remarkable (47%) reduction in LDL-C, producing an LDL-C of 227 mg/dL, without myalgias.

Since fluvastatin XL 80 mg is a single-dose drug, this patient is someone for whom combined therapy—adding either a bile acid binder such as colesevelam hydrochloride (Welchol) (22) or an intestinal cholesterol receptor inhibitor such as ezetimibe (Zetia) (23, 24)—can further reduce LDL-C levels by another 18–40% on average. She was placed on ezetimibe 10 mg, and her LDL-C dropped 30% to 160 mg/dL, our goal for her. She is a hyperresponder to LDL-C-lowering therapy with both fluvastatin XL and ezetimibe. Her situation illustrates the fact that many persons with higher LDL-C levels at baseline will respond better to therapy than those with lower levels. Thus, what would at first seem an impossible lipid-altering task turns out not to be so.

Case 4: 66-Year-Old Woman (Fig. 5)

The first step in this case is simply to maximize the strength of the drug that she is on; fortu-

Case 4 66 year-old woman

Angina at age 55
Coronary angioplasty with stent at age 65

Pravastatin, lovastatin, and fluvastatin not potent enough
Atorvastatin 40 mg caused severe myalgias
On simvastatin 40 mg when first seen in referral

TC	TG	HDL-C	LDL-C	T/HDL-C	
288	227				Atorva 40 Simva 40
201	123	50	126	4.2	
230	146	48	153	4.8	Simva 80
175	113	46	106	3.8	Colesevelam (Welchol) 3 tabs BID
172	132	56	90	3.1	

Fig. 5. Case 4: 66-year-old woman
Atorva = atorvastatin (Lipitor) mg qd, Simva = simvastatin (Zocor) mg/qd
For all other abbreviations, see Fig. 1.

nately, 80 mg of simvastatin did not elicit the myalgias seen with other statins she had used. Like ezetimibe, bile acid binders can be used to increase the LDL-C lowering of a statin. In this case, it decreased LDL-C another 25%, into the LDL-C goal range desired for someone with known CHD. Colesevelam has become a welcome anion binder in the gut, because it is in pill rather than powder form and is more specific for binding bile acid anions than other medications in anionic form. Hence, patients no longer need to worry about decreased absorption of thyroid hormone, digoxin, some antibiotics, and some vitamins when using less specific bile acid binders such as cholestyramine and colestid. However, patients still must take 6 large tablets daily. The cost of bile acid binders is approximately twice the cost of ezetimibe for the same LDL-C-lowering power. On the other hand, bile acid binders are truly nonsystemic, because there is no gastrointestinal absorption, they have been shown to reduce coronary heart disease events, and they have shown no long-term toxicity in randomized, controlled trials. Since ezetimibe is absorbed and excreted through the biliary tree, there are low plasma levels and the predicted long-term safety of this medication awaits confirmation.

C. Be cautious with patients with severely reduced HDL-C levels and use combined therapy to raise HDL-C and lower LDL-C levels.

Case 5: 54-Year-Old Male (Fig. 6)

Case 5 54-year-old male

Healthy, sedentary

Father had MI in his early 60's

Discontinued smoking 16 years earlier
No history of diabetes
Hypertension for 13 years on a calcium channel blocker
History of uric acid stones on Allopurinol 150 mg qd

HT: 5' 11" WT: 235lbs IW: 178 lbs
BP: 148/86 mm Hg Waist circumference: 40.5 inches
Lipid/laboratory values (mg/dL)

	TC	TG	HDL-C	LDL-C	T/HDL-C ratio	Glucose
6/00	147	213	19	85	7.7	77
8/01	145	160	16	97	9.1	150
9/02	145	134	18	100	8.1	150

Lp(a) = 30 mg/dl Homocysteine = 11.4 mm/L

Fig. 6. Case 5: 54-year-old male
For all abbreviations, see Figs. 1 and 2.

What are the risk factors? What is the LDL-C goal? How should he be treated?

This patient originally had the metabolic syndrome but subsequently developed the hyperglycemia of type 2 diabetes. Without lipid-altering medications, he already has an LDL-C < 100 mg/dL. Should the physician add a statin to reduce LDL-C further? This question has been answered by the Heart Protection Study (2), an important randomized, controlled trial of simvastatin 40 mg qd vs. placebo in patients at high risk for subsequent cardiovascular events. ("At high risk" is defined here as having CHD, cerebrovascular disease, or peripheral vascular disease; hypertension; or diabetes, with a baseline total cholesterol > 135 mg/dL.) Major coronary events of MI and cardiovascular disease death were reduced by 25% in those patients placed on simvastatin 40 mg, even with baseline levels of LDL-C < 100 mg/dL.

But what about the low HDL-C? Should it be increased? There is growing evidence for increasing HDL-C to add a further preventive effect to the lowering of LDL-C. The HDL-Atherosclerosis Treatment Study (HATS) (25) was a three-year quantitative coronary angiographic trial of simvastatin 40 mg plus niacin to increase HDL-C by approximately 10 mg/dL, compared with placebo, in 160 persons with CHD. Qualifying HDL-C had to be < 35 mg/dL in men with triglycerides < 400 mg/dL, levels that would qualify our patient. In the placebo and simvastatin/niacin groups not on antioxidant vitamins, mean LDL-C levels were 116 and 75 mg/dL and mean HDL-C levels were 34 and 40 mg/dL, respectively. In the placebo group, the mean percentage of stenosis from 9 proximal lesions increased 3.9% compared with a decrease of 0.4% in those on the simvastatin-niacin combination (p<0.001). More remarkable for a trial not powered to show differences in clinical events, 9 of 34 patients in the placebo group experienced CV death, MI, or revascularization compared with only 1 patient in the combination group, an 89% decrease (p=0.04). Such a small trial provides no definitive clinical evidence but serves to strongly promote the hypothesis that the HDL raising may be very important clinically and may add to the preventive effects of simply lowering LDL-C.

The cardiovascular preventive benefits of niacin were first demonstrated in 1975 in the Coronary Drug Project, in which men who had a history of previous myocardial infarction and were taking 3 grams of niacin daily, showed a 27% decrease in MI at 5 years (from 12.2% to 8.9%, p<0.005) compared with those on placebo (26). The same study demonstrated an 11% decrease in all-cause mortality measured 9 years later, after the formal study had ended (52.0% vs. 58.2%, p<0.001) (27).

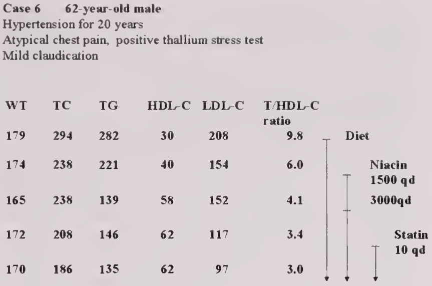
Niacin comes in immediate-release and sustained-release forms, the former causing more flushing reactions, the latter less-beneficial lipid effects and more hepatotoxicity, especially at high doses (28). An intermediate-release form, niacin SR (Niaspan), is also available and seems to give the excellent lipid effects of immediate-release niacin without the hepatotoxicity of the sustained-release forms (29). Unfortunately, it is significantly more expensive. No-flush inositol preparations are ineffective because they contain none of the active free nicotinic acid (30). Niacin can raise uric acid levels and precipitate gout, but hopefully this patient would not be affected, since he is already on allopurinol.

In the course of being evaluated for his lipid abnormalities, the patient sustained an inferior wall MI. He was lost to follow-up, but hopefully he is currently on a statin and a niacin preparation, as in the following case.

Case 6: 62-Year-Old Male (Fig. 7)

Hypertension for 20 years; atypical chest pain; positive thallium stress test; mild claudication.

For this patient, niacin reduced triglycerides and LDL-C somewhat and increased HDL-C significantly. The statin was added to reduce LDL-C into our goal range of < 100 mg/dL. Niacin will also increase the size of LDL particles (31), making them less atherogenic. Niacin is also one of the few medications we have which reduce Lp(a). However, there have been no clinical trials to show that reducing Lp(a) will additively reduce risk. The Scandinavian Simvastatin Study (4S) demonstrated that the adverse predictive value of increasing quartiles of baseline Lp(a) for future MI and cardiovascular death tended to be lost when the high levels of LDL-C in that trial (150–250 mg/dL, mean baseline 188 mg/dL) were lowered with simvastatin to an average level of 122 mg/dL (32). A similar loss of adverse predictive value of Lp(a) was shown with substantial reduction of LDL-cholesterol in the Familial Atherosclerosis Treatment Study (33). Hence a prudent management for cardiovascular risk associated with an elevated Lp(a) level > 30 mg/dL (highest quintile of population) and an elevated LDL-cholesterol based on the cited clinical evidence is simply to reduce the LDL-cholesterol by 30 to 40% to a value < 130 mg/dL.



Case 6 62-year-old male
Hypertension for 20 years
Atypical chest pain, positive thallium stress test
Mild claudication

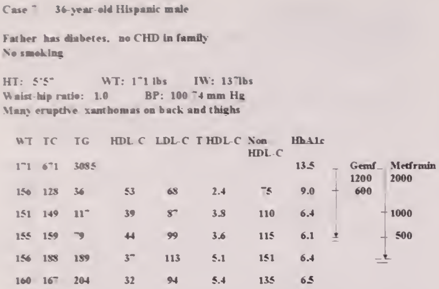
WT	TC	TG	HDL-C	LDL-C	T/HDL-C ratio	
179	294	282	30	208	9.8	Diet
174	238	221	40	154	6.0	Niacin 1500 qd
165	238	139	58	152	4.1	3000qd
172	208	146	62	117	3.4	Statin 10 qd
170	186	135	62	97	3.0	

Fig. 7. Case 6: 62-year-old male
For all abbreviations, see Figs. 1 and 2.

D. For patients with diabetes mellitus, and potentially those with the metabolic syndrome, strongly consider the use of fibric acid therapy alone or in addition to statin therapy.

Case 7: 36-Year-Old Male, Referred for Eruptive Xanthoma (Fig. 8)

This young man was referred by a dermatologist when, at the sudden onset of severe hypertriglyceridemia secondary to the hyperglycemia of type 2 diabetes, the patient developed eruptive xanthoma. The most effective pharmacologic therapies for severe hypertriglyceridemia are fibric acid and niacin (6). Triglyceride values above 1000 mg/dL often represent the presence of chylomicrons and indicate increased risk for chylomicron-induced pancreatitis. While lowering triglycerides with gemfibrozil, the patient also eliminated concentrated sweets from his diet, began exercising, and was also started on metformin. This regimen increased insulin sensitivity, reduced glucose levels and hemoglobin Al_c ($HbAl_c$) into a more



Case 7 36-year-old Hispanic male

Father has diabetes. no CHD in family
No smoking

HT: 5'5" WT: 171 lbs IW: 137lbs
Waist-hip ratio: 1.0 BP: 100/74 mm Hg
Many eruptive xanthomas on back and thighs

WT	TC	TG	HDL-C	LDL-C	T HDL-C	Non HDL-C	HbA1c	Gemf	Metfrmin
171	671	3085					13.5	1200	2000
156	128	36	53	68	2.4	75	9.0	600	
151	149	117	39	87	3.8	110	6.4		1000
155	159	79	44	99	3.6	115	6.1		500
156	188	189	37	113	5.1	151	6.4		
160	167	204	32	94	5.4	135	6.5		

Fig. 8. Case 7: 36-year-old Hispanic male
Non-HDL-C = TC minus HDL-C, HbAlc = glycosylated hemoglobin (%), gemf = gemfibrozil (mg qd), metfrmin = metformin (mg qd).
For all other abbreviations, see Fig. 1.
All lipid values in mg/dL.

normal range, and helped with weight loss, thereby reducing triglyceride levels.

Fortunately, the patient was quite compliant with the regimen and immediately began losing weight, with remarkable corrections in triglyceride levels and steady drops in hemoglobin A1c, even as both gemfibrozil and metformin were decreased and then stopped. In his case, the NCEP ATP goal for non-HDL-C (30 mg/dL greater than the LDL-C goal) was < 130 mg/dL (6). As he gets older, and his control of diet, weight and activity backslides a bit, he will inevitably be back on these medications. Because of his low HDL-C and moderately increased triglycerides, giving him a total cholesterol (TC)/HDL-C ratio > 5.0, one cannot feel very confident about his long-term prevention of CHD and could easily argue for restarting a fibric acid or starting a statin to prevent premature atherosclerosis.

The Veteran's Administration High Density Lipoprotein Intervention Trial (VA-HIT) (34) demonstrated that gemfibrozil therapy 600 mg bid reduced CHD death plus nonfatal MI by 22% in men with previously documented CHD and TG < 300 mg/dL, HDL-C ≤ 40 mg/dL and LDL-C ≤ 140 mg/dL over a 5-year period. An important finding in this study was that the effects were more dramatic in those with diabetes than in those without it (35). The number of patients needed to treat in order to prevent one CHD death or MI in the overall population was 23, but in the diabetic population it was only 12. In addition, in those without diabetes, gemfibrozil was effective in reducing CHD risk in the top quartile of insulin resistance, but not in the three lower quartiles of insulin resistance. Gemfibrozil would seem to be most effective in preventing CHD in those with the insulin resistance/diabetic dyslipidemia secondary to high triglycerides, low HDL-C, and small LDL particle size.

To prevent CHD, the American Diabetes Association (ADA) recommends that statins be the first drug of choice for patients with diabetes (36). ATP III recommends an LDL-C goal of less than 100 mg/dL. But in this case the use of gemfibrozil resulted in an LDL-C < 100 mg/dL, and the VA-HIT study showed that gemfibrozil is cardioprotective in persons with type 2 diabetes or insulin resistance. Had his triglycerides remained elevated at greater than 400 mg/dL even with glucose control, one could argue that a fibric acid would be the more efficacious drug for his lipid abnormalities. But his triglycerides and glucose seem in fairly good control with lifestyle changes, and thus it is reasonable in his case to follow the evidence-based guidelines of the ADA and the recent NCEP guidelines, and place him on a moderate-dose statin for long-term CVD prevention.

Case 8: 63-Year-Old Woman (Fig. 9)

This patient has well-controlled diabetes, and coronary heart disease, and is on a reasonable statin dose with hypertriglyceridemia still inadequately treated (367 mg/dL). Investigators in the Diabetes Atherosclerosis Intervention Study (DAIS) randomly assigned 418 persons with type 2 diabetes and moderate elevations in LDL-C (135–175 mg/dL) and triglycerides (150–465 mg/dL), and with at least one visible coronary angiographic lesion, to the fibric acid, fenofibrate (Tricor), and followed them for 3 years (37). The fenofibrate group, compared with the placebo group, showed significant decreases in coronary lesions, with a smaller increase in percentage diameter stenosis (2.11 vs. 3.65%, p=0.02) and a significantly smaller decrease in minimum lumen diameter (–0.06 vs. –0.10 mm, p=0.029). Participants taking fenofibrate had fewer CHD clinical events (death, MI, percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass graft [CABG]) than those taking placebo (38 vs. 50), but the study was not powered to show this as a statistically significant difference.

The clinical issue for this woman is whether to increase her statin dose to achieve a total cholesterol of 204 mg/dL and triglycerides of 367 mg/dL, add a fibric acid to her statin, or do both. In this case the addition of fenofibrate to atorvastatin vastly improved her lipid profile, but even with the results above one wonders whether she is adequately protected. Results of REVERSAL and PROVE-IT (3, 4) would suggest that her LDL-C is

Case 8 63-year-old woman

HTN for 25 years, on 2 medications CABG 5 years earlier
Diabetes, on oral agents with HbA1c = 6.9%
No smoking, no hormone replacement therapy
Mother had HTN, died age 48 CVA

HT: 5'2" WT: 145 lbs IW: 123 lbs
Waist-hip ratio: .94 BP: 155/88 mm HG

TC	TG	HDL-C	LDL-C	T/HDL-C	Non-HDL-C		
						Atorv 20	
247	1460	27	---	9.1	220		
204	367	---	---	---	---		Feno 160
187	81	56	115	3.3	131		
188	162	53	103	3.5	135		

Fig. 9. Case 8: 63-year-old woman
Atorv = atorvastatin (Lipitor), Feno = fenofibrate (Tricor), non-HDL-C = TC minus HDL-C, HbAlc = glycosylated hemoglobin (%).
For all other abbreviations, see Fig. 1.

inadequately controlled and that an increase in atorvastatin is needed, along with the addition of fenofibrate.

Can one achieve additional beneficial effects for patients with diabetes and CHD, or at high risk for CHD because of other risk factors, by adding a fibric acid to a statin? The question will be answered in several years in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (which will not finish recruitment until mid-2005 and is expected to have an average follow-up of 4.5 years). Six thousand subjects in the lipid arm of the trial will be randomly assigned to simvastatin 20 mg or simvastatin 20 mg combined with fenofibrate 160 mg qd. The diabetic subgroups of the TNT and SEARCH trials should provide evidence on how low the LDL-C should be targeted when a statin is used alone.

With this patient, there is also the issue of how we determine the adequacy of treatment for someone with diabetes and CHD. Since such patients often have lipid patterns based on small LDL particles, an LDL-C < 100 mg/dL may indicate someone with excess small LDL particles, still at risk for further plaque progression (38). One could set a goal of approximately 70 mg/dL for LDL-C, as discussed in Case 1 above and as recommended as a treatment option for persons with diabetes and CHD. And yet for someone with diabetes or the metabolic syndrome and CHD, this may be inadequate lipid-altering therapy.

Three newer lipid parameters to assess adequacy of treatment have been suggested: non-HDL-C, LDL particle number and Apo B. Non-HDL-C as a measure of Apo B in all fasting atherogenic lipoprotein particles has been suggested by NCEP ATP III as a secondary target of therapy in those patients with triglyceride levels > 200 mg/dL. In persons with established CHD in the Bypass Angioplasty Revascularization Investigation (BARI) trial, non-HDL-C was shown to be a better predictor of nonfatal MI and angina over 5 years than total, HDL and LDL cholesterol levels (39). In American Indians with diabetes, but without cardiovascular disease, in the Strong Heart Study, non-HDL-C was also shown to be a better predictor of combined fatal and nonfatal cardiovascular disease and coronary heart disease than LDL-C and triglycerides (40).

Another measure of atherogenic particles is the level of Apo B. One Apo B is associated with each LDL, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and Lp(a) particle. Since the half life in the circulation of LDL particles is substantially greater than that of the other Apo-B-containing particles, Apo B levels are a good surrogate for LDL particle numbers. Apo B levels have been better predictors of long-term risk for vascular disease in several large prospective studies, and on-trial Apo B levels have been better predictors of subsequent coronary events than LDL-C levels in several statin-versus-placebo, randomized controlled clinical trials (41). A recent study comparing non-HDL-C and Apo B, suggests that non-HDL-C is equivalent to Apo B in diabetic persons with triglycerides higher than 200 mg/dL, but substantially underestimates risk in those with lower triglyceride levels (42, 43).

The Canadian lipid guidelines for persons with CHD target an Apo level < 90 mg/dL, this being the 20th percentile of the Canadian population (44). The Chairman of the NCEP ATP III has also suggested an Apo level < 90 mg/dL (45). The approximate 20th percentile for men and women in the Framingham Offspring population (46) and the NHANES sample of the United States population is < 80 mg/dL (47). Thus, depending on one's aggressiveness in Apo B lowering, one could aim for < 90 or < 80 mg/dL.

Liposcience measures LDL particle number by nuclear magnetic resonance spectroscopy of lipid particles, giving both an LDL size and particle number. LDL-C < 100 mg/dL and LDL particle number < 1100 nmol/L represent the lowest quintile in the Framingham Offspring Study (48). Thus, in those with type 2 diabetic dyslipidemia consisting largely of excessive small LDL particles, an LDL particle number < 1100 nmol/L may represent a better target than an LDL-C goal of 100 mg/dL, and < 800 nmol/L may represent a more aggressive target than an LDL-C goal of < 70 mg/dL. Yet none of these newer lipid goals have been compared in clinical prevention trials. Thus, one is left with several highly suggestive but unproven approaches if one wishes to go beyond the newer ATP III goal of an LDL-C < 70 mg/dL in a diabetic patient with coronary heart disease.

In conclusion, we have considered several cases with common but provocative cardiovascular and lipid histories and findings, and attempted to expand our thinking about their management. The future of preventive lipid management will probably include better assessment of risk for those patients without clinical CHD, more sophisticated lipid testing with clearer and more evidence-based therapeutic goals, increased use of combined lipid-altering agents, and better methods for improving patient compliance with such regimens.

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Grand Rounds

A Caring Partnership:

Can We Gain Control?

John A. Balint, M.D.

Abstract

Background: The health care system in the United States is in trouble. Patients and physicians are becoming increasingly unhappy with the system. There has been a progressive deterioration in trust in the system and in patient-doctor interactions.

Methods and Results: The history of the evolution of medicine as a profession over the past 350 years is briefly reviewed. The forces that have changed a paternalistic, but caring, system into one that is no longer paternalistic, but also less caring, are discussed. It is suggested that the current market-driven, industrial model is failing both patients and physicians, and that it is too costly.

Conclusion: The case is presented for patients and physician to join forces to work for reforms of the system, to encourage more physicians to take up careers in primary care, to fund health insurance for the uninsured, and to subsidize the education of future physicians. These approaches should help restore trust and a caring partnership between patients and their physicians. This partnership is necessary for attaining the reforms suggested.

Key Words: Patient-physician relationship, health care system, health care reform.

Introduction

Over the past 20 years or more dissatisfaction with health care in the United States has been increasing, among both patients and physicians (1, 2). Patients are frustrated by the conflict between the promise of the new technology and its increasingly high cost (1). They also note the change in the physician-patient interaction, which they perceive as being less personal and increasingly brief (2). Physicians have a similar sense of frustration with a health care system that they feel forces them to be "double agents," always asked to balance patient needs against societal and financial priorities, as represented by insurance carriers (3, 4). While these issues have become more sharply defined over the past ten years, concerns about changes in the patient-doctor relationship have been voiced by physicians for more than two generations (5, 6). In this essay I will review the evolution of our present malaise and suggest a way out of our troubles.

Where We Were

Medicine as a scientific discipline began to evolve some 350 years ago with the publication of William Harvey's *De Motu Cordis*. This was followed by the remarkable success of Herman Boerhaave as a professor of medicine at the University of Leiden in Holland from 1701 – 1738 (7). His teaching style attracted students from Britain and Europe. His influence was thus widespread. At about the same time, Thomas Sydenham (1624 – 1689) established the crucial importance of bedside observation as the basis of clinical diagnosis and, therefore, of case management. It was based on Sydenham's precepts that the great physicians of the 19th century, such as Laennec, Bright, Addison and others, described the disorders which still carry their names.

The 19th century saw the evolution of microbiology by such great men as Koch. A century earlier Jenner had established vaccination for the prevention of smallpox, and Lind had demonstrated

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Professor of Medicine, Director, Center for Medical Ethics, Albany Medical College, Albany, NY.

Address all correspondence to John A. Balint, M.D., Center for Medical Ethics, Mail Code 153, Albany Medical Center, 47 New Scotland Avenue, Albany, NY 12208; email: balintj@mail.amc.edu

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that fresh fruit juice prevented scurvy. In 1847 Withering recognized the value of digitalis in treating heart failure. These were the first demonstrations that it was possible to prevent disease or moderate its ill effects. The first medical organization to set out a code of medical ethics was the American Medical Association (AMA), in 1849. The end of the 19th century saw the establishment of the Johns Hopkins University and School of Medicine, with William Osler and W.S. Halstead as chairs of the medicine and surgery departments, respectively. This marked the start of the movement towards academic health science centers in the US, which was followed by European and British universities. The high standards set by such institutions and the steady evolution of the scientific basis of medical care established the conditions for growing public trust in the work of physicians.

The relationship of patients to physicians was based on this trust. For more than half a century patients accepted the paternalistic model of the patient-physician interaction handed down over the centuries from the time of Hippocrates and Plato (4). The evolution of clinical and basic science since the time of Harvey had laid the foundation of medicine as a true profession. With a definable scientific basis, a body of clinical knowledge and the establishment of accredited educational institutions, society accepted the right of the medical profession to govern itself. In return for this right the members of the medical profession were expected to provide care for all comers to the best of their ability. Thus, a social contract evolved which patients and physicians accepted. Yet although medical science was advancing, effective treatments were slower to develop. Thus, while our ability to make diagnoses improved and we were able to offer prognoses and sometimes (most often in surgery) cures, patient care based on good supportive relationships between physicians and patients remained the basis of the care of the patient (6).

Where Are We Now?

After World War II we saw a dramatic growth in the science and technology of medicine. There was the discovery of antimicrobial agents that replaced sulfonamides, automated analysis for blood chemistries, cardiac catheterization, fiberoptic endoscopy, computed tomography (CT) scanners, magnetic resonance imaging (MRI) and minimally invasive surgery. The advances in pharmaceutical science brought a plethora of new treatments, with new drugs that were often curative. Now, new genetic analysis and perhaps genetic therapy are on the horizon. These developments have spurred the growth of subspecialties in all the major branches of medicine, promising more prestige and higher incomes for specialists. At the same time physicians began to work in larger practices in medical offices, and no longer as solo practitioners seeing patients in consulting rooms that were in their own homes (5). Indeed physicians, as their incomes grew, moved into the suburbs, away from many of their patients. This specialization and geographic separation have contributed to a gradual loosening of the patient-physician relationship (5).

During this same period, society was also changing, under the influence of social forces such as the civil rights movement and the women's rights movement. These and other rights movements led to increasing emphasis on individual autonomy for other social groups, including medical patients. And patient autonomy was stimulated by other factors, such as the failure of clinical investigators, in an era of rapidly developing science and technology, to ensure that subjects of investigation were fully informed of the risks and benefits of interventions (8). This in turn led to commissions appointed by the President or Congress and the courts to examine how the profession conducted itself (8). These examinations resulted in commission reports and court judgments requiring the development of national standards for informed consent for clinical investigations (8). In addition the problem of medical error was highlighted by the Harvard Study in the early 1980s. And the quality of hospital care in New York State was the subject of an investigation undertaken at the request of Dr. David Axelrod, the New York State Commissioner of Health. These developments added to the erosion of trust by patients in the health care system as a whole.

These societal and professional developments occurred during a period when the rising costs of health care greatly exceeded the inflation rate in the general economy. In the late 1970s and early 1980's general inflation was 8–10% annually while health care costs rose by 14–16%. Physician incomes were also rising, as were health insurance rates. This led in turn to attempts to develop both not-for-profit and for-profit health maintenance organizations (HMO) and managed care organizations (MCO) as a way of controlling costs. While these interventions helped for a while, they were soon overtaken by events. Despite efforts to make health care a market commodity and encourage privatization, cost pressures continued. By 2004, health care expenditures accounted for 14–15% of gross domestic product (up from 6–7% in 1980) and amounted to $1.55 trillion annually, which represents $5,400.00 per person annually. Furthermore, while the national inflation rate is now about 2.5 – 3%, health care inflation increases are 10 – 12% (9). Yet we now have about 45 million uninsured, 15 – 20 million temporarily without insurance, and a further 20 million who are underinsured (10 – 14). Our health care costs are more than twice as high as those of any other industrialized nation. However, measured by World Health Organization standards, we rank 32nd in health outcomes in the world, including life expectancy at birth, infant mortality and immunization rate, among other measures of health.

We have allowed our profession and our health care system to become an industry that is market driven. Many patients and physicians are unhappy. The societal problems of the uninsured are huge, in terms of increased suffering and increased cost. Efforts at cost control lead to covert rationing, because insurers disallow certain treatments or investigational interventions, or impose time-consuming prior certification requirements to discourage their use. This leads to increasing stress on patients and physicians. A consequence of these influences may be an increase in malpractice litigation.

Where Do We Go from Here?

It seems to me that the present system of health care is failing its beneficiaries, i.e., the patients, as well as the professionals, physicians, nurses and others working in it. This failure demonstrates that health care does not flourish as a market commodity, since it excludes millions from enjoying its remarkable potential benefits. Even those with access to services find it impersonal and frustrating. It is, therefore, time for a change. But physicians, even with the support of other health care professionals, cannot achieve significant change without the help of our patients — numbers really count. We need to form an alliance with our patients to attain that goal (4). This will require restoring an effective, educated trusting relationship between patients and physicians (4).

The foundations of such a caring partnership are the well-established ethical principles on which good medical practice has been based for centuries:

- Beneficence: caring for the patient, altruism, guidance and advocacy.
- Non-maleficence: do no harm, ask, "What should we do?" not just "What can we do?"
- Justice: provide needed care for all; health care as a communal good.
- Respect for person: regardless of status, culture, religion or race.

The first requirement for ensuring that these principles guide our practice is that we must ensure understanding of the fundamentals of good patient-physician relationships that will truly foster a caring partnership. Over the past 50 years a number of authors, including Szasz and Hollender, Siegler, Pellegrino and Thomasma, Engel, Emmanuel and Michael Balint, have described various models of this relationship. All emphasize mutual trust, understanding and partnership. These models have been previously reviewed (2, 4). They are in striking contrast to the model offered by Engelhardt and Rie, which is based on a libertarian and market-based system (14), which in my view has clearly failed. The model described by my father, Michael Balint, based on research and training seminars with general practitioners in the UK, is the one that most clearly describes the dynamics of the patient-physician relationship (15). I believe it is a model that points the way forward. This model identifies four basic features of the relationship. The first reinforces the old saying "Physician know thyself," so important for understanding how we react to different persons. The second requires that the physician establish the "deeper diagnosis," that is, the medical, social and personal issues of the patient. This is very much along the same lines as described by Jonsen, Siegler and Winslade in their book *Clinical Ethics* as the "four boxes" (16). The third is the physician's "apostolic function" (15), which calls for the education of the patient about his/her illness, and how to deal with it. This must be accompanied by the fourth component of mutual education leading to the "mutual investment company" or caring partnership. This in turn allows patient and physician to address management issues founded on evidence-based medicine and thus more prudent use of health care resources. A trusting partnership is the fundamental basis for such discussions. Arriving at a trusting partnership takes time. The physician and patient need to learn how to use multiple, relatively brief visits to build the understanding that is the essential basis for attaining this goal.

To bolster the evolution of a caring and trusting partnership, physicians, their professional societies and the health care system must take steps to address the problem of medical errors. Physician leadership in this area is critical to restoring trust in the system as a whole while developing the partnership between individual patients and their physician. Physicians will also need to influence their professional societies to take up public advocacy for better patient access to affordable health care and drugs. Too often at the present time, our professional societies lobby for the benefit of their members only. A few, such as the American College of Physicians, have been a strong lobby for patient needs. We need others to join them for our profession to regain the societal respect it must have to succeed in restoring the caring partnership on a broad basis.

To attain a health care system that measures up to the standards noted above, we will need to increase the number of physicians providing primary care, whether as internists, family physicians or other primary care specialists (17–22). This will require cooperation among current rivals (19), changing residency education programs (22) and reforming payment for primary care (21), as was recently suggested by the Society for General Internal Medicine (23). In order to change the ratio of generalists to subspecialists (as suggested above) and provide insurance coverage for those currently uninsured so that they can gain access to care calls for fundamental changes in our present system. Currently the administrative costs in the US health care system are about 25 cents on the dollar compared to Canada or Europe, where it is 7–10%. Medicare's administrative costs are similar to those in Canada. If we could cut the administrative overhead in the US by half we could save about $180–190 billion annually, based on current reported costs (9). The estimated cost of providing basic health insurance to the uninsured is $75–85 billion, so the savings in administrative costs could readily cover these expenses and leave resources available for other improvements in the system. These could be used to make careers in primary care more readily attainable for new graduates of our medical schools, as I will discuss below.

If we are to achieve the changes outlined above, we will need to work in a caring partnership with our patients to change the national view of health care from that of a market-driven industry to one that recognizes health care as a social good and obligation, like public education, sewage systems and national defense. Acceptance of this view will not come easily, but that major change can be achieved has been shown in Oregon (24) and Maine (25). In both of these states the process involved extensive public discussion. To allow new graduates to pursue careers in primary care medicine, which so many applicants to medical school would like to be able to do, we will need to remove several economic barriers. The average level of debt carried by medical school graduates is well in excess of $100,000. The US is the only industrialized democracy that does not subsidize medical education. If we were to apply the savings realized by reduction of administrative overheads in health insurance costs, discussed above, to paying for the education of future physicians, the economic barriers could be removed. In return, we may wish to consider some form of salaried health service. Several good models exist in Europe, as well as in the US, such as the VA Medical System, the time-honored academic medicine system and such staff model HMOs as Health Care of Puget Sound or the Kaiser Permanente System. At the same time we should examine ways of rewarding good, cost-effective care by innovative approaches such as the new program adopted by the National Health Service in the UK (26, 27). Any such system must ensure transparency, so that all participants recognize the rationale for particular management decisions (28). "The mutual investment company" concept discussed above would allow physicians to discuss such decisions more readily with their patients. Based on all those discussions between patient and physician, the physician may have to be willing to advocate for a deviation from the usual treatment, based on the special needs of a particular patient.

Can these goals be achieved? Maybe that will only happen if we have a catastrophic crisis in health care. I hope that that can be avoided if we as a profession can, even within current constraints, work towards a caring partnership with our patients and towards the acceptance of the principle of health as a societal good. That is a goal worth striving for. We will, as noted, need allies in order to succeed. Those allies are our patients. Our guide in this endeavor should be Osler's injunction, "You are in this profession as a calling, not as a business, as a calling which exacts from you at every turn self-sacrifice, devotion, love and tenderness to your fellow man" (29).

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Current Management of Ischemic Mitral Regurgitation

Farzan Filsoufi, M.D., Sacha P. Salzberg, M.D., and David H. Adams, M.D.

Abstract

Severe coronary artery disease and myocardial infarction can be complicated by ischemic mitral regurgitation (IMR). IMR results from left ventricular remodeling after myocardial infarction and in rare instances can accompany acute ischemia. A better understanding of the pathophysiology of IMR and increased awareness of its negative impact on long-term survival explain the recent rise in the number of patients referred for surgical correction of IMR at the time of coronary revascularization. The most common mechanism of IMR is Carpentier's type IIIb dysfunction, for which an undersized remodeling annuloplasty is the treatment of choice. In this article we define ischemic mitral regurgitation and review its pathophysiology, clinical presentations, diagnosis, indication for surgery, and management.

Key Words: Mitral regurgitation, ischemic cardiomyopathy, coronary artery disease, mitral valve surgery, coronary artery bypass grafting.

Introduction

Severe coronary artery disease and myocardial infarction (MI) can be complicated by mitral regurgitation (MR). Commonly referred to as "ischemic MR" (IMR), in most instances it results from either left ventricular remodeling following myocardial infarction, or less frequently, from acute ischemia. This entity should be distinguished from ischemic cardiomyopathy and associated MR due to other underlying etiologies such as degenerative mitral valve disease, rheumatic disease, and endocarditis. For several years, because of a lack of understanding of the precise pathophysiology of IMR, most of the medical and surgical literature has failed to distinguish between these different clinical entities. Until recently, most clinical series have included heterogeneous groups of patients and produced contradictory results which have led to unclear conclusions and guidelines with respect to medical and surgical management of these patients. More recently, laboratory research and clinical outcome analysis have contributed significantly to improving our understanding of this complex disease and its medical and surgical management. This improved understanding of the pathophysiology of ischemic MR and the increased awareness of its negative impact on long-term survival explain the recent rise in the number of patients referred for surgical correction of IMR at the time of coronary revascularization. In this article we will review IMR with regard to its pathophysiology, clinical presentations, diagnosis, indication for surgery, and management.

Definition of IMR and Carpentier's Functional Classification of MR

The understanding of mitral valve pathology is facilitated by the use of the "pathophysiological triad" first described by Carpentier (1). This triad is composed of etiology (cause of the disease), valve lesions (resulting from the disease) and

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From the Department of Cardiothoracic Surgery, Mount Sinai Medical Center, New York, NY.

Address all correspondence to Farzan Filsoufi, M.D., Director Cardiac Valve Center and Assistant Professor, Department of Cardiothoracic Surgery, Box 1028, Mount Sinai Medical Center, 1 East 100th Street, New York, NY 10029; email: Farzan.Filsoufi@mountsinai.org

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valve dysfunction (resulting from the lesions). These distinctions are relevant because long-term prognosis depends on etiology, whereas treatment strategy and surgical techniques depend on valve dysfunctions and lesions, respectively (2). This classification is based on the opening and closing motions of the mitral leaflets (Fig. 1). Patients with type I dysfunction have normal leaflet motion, and MR is the result of annular dilatation. There is increased leaflet motion in patients with type II dysfunction, with the free edge of at least one of the leaflets overriding the plane of the annulus during systole (leaflet prolapse). The most common lesions responsible for type II dysfunction are chordal elongation or rupture, and papillary muscle elongation or rupture. Finally, type III dysfunction results from restricted leaflet motion, with the free margins of portions of one or both leaflets pulled below the plane of the annulus, into the left ventricle, thereby reducing leaflet mobility and coaptation during systole and leading to MR. Patients with type IIIa dysfunction have restricted leaflet motion during both diastole and systole. The most common lesions are leaflet thickening/retraction, chordal thickening/shortening or fusion, and commissural fusion. In type IIIb dysfunction, there is restricted leaflet motion during systole. Left ventricular dysfunction and dilatation with apical papillary muscle displacement causes this type of valve dysfunction.

Ischemic MR can result from type I, II or IIIb dysfunction (Table). Type I dysfunction with annular dilatation occurs in basal MI. Type II dysfunction results from papillary muscle rupture (3–5). Carpentier's type IIIb dysfunction is the most common form of ischemic MR (6–11). A set of criteria is suggested in order to precisely define type IIIb ischemic MR (12): significant symptomatic multi-vessel coronary artery disease, with or without documented prior MI, *and* at least grade 2+ MR, documented on a preoperative echocardiogram or ventriculogram. In addition, the leaflet structure should be normal, there should be no leaflet prolapse (type II), in absence of any mitral stenosis (6).

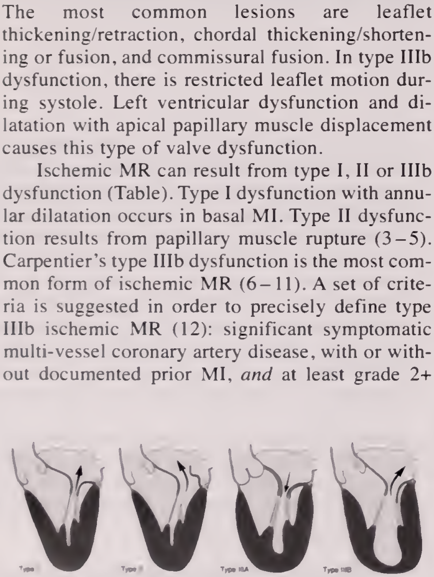

Fig. 1. Carpentier's functional classification. Type I: normal leaflet motion Type II: increased leaflet motion (leaflet prolapse). Type III restricted leaflet motion: A: during diastole and systole, B during systole only.

The arrow shows the direction of the jet in types I, II and IIIB. It shows the association of some degrees of mitral stenosis in type IIIA.

TABLE 1
Pathophysiological Triad in Ischemic MR

Dysfunction	Lesions	Chronic / Acute
Type I	Annular dilatation	Chronic
Type II	Papillary muscle rupture	Acute
	Chordal rupture	Acute
	Papillary muscle elongation	Chronic
Type IIIb	Papillary muscle displacement Leaflet tethering	Acute or chronic

Type IIIb Ischemic MR

Pathophysiology

Normal mitral valve function involves a complex three-dimensional interaction between the leaflets, annulus, subvalvular apparatus and left ventricular wall. Several anatomic and pathophysiological changes are associated with the pathogenesis of ischemic MR. They include ventricular changes (wall motion abnormalities, dilatation with increased sphericity), sub-valvular changes (papillary muscle infarction, displacement or tethering) and annular changes (distortion, dilatation). The initiating insult in IMR is ventricular, specifically left ventricular remodeling following myocardial ischemia or infarction. This remodeling converts the shape of the left ventricle from ellipsoidal to spherical (increase in sphericity index), which may subsequently lead to regional annular and subvalvular distortion and ultimately to poor leaflet coaptation.

Papillary muscle displacement plays a critical role in the pathophysiology of IMR. The tethering distance has been correlated to the severity of IMR (13–15) . Papillary muscle tethering leads to "apical tenting" of the leaflets (restriction of the motion of the free margins of the leaflets), which prevents them from rising to the plane of the annulus to coapt with one another. This has been well documented using quantitative echocardiographic methods in a clinical setting (12). Tethering on the secondary chordae can result in a "sea-gull" deformation of the body of the leaflet, further impairing coaptation. Finally, annular dilatation is a common finding in clinical cases of chronic IMR. However, the degree of dilatation can vary and does not necessarily correlate with the degree of MR. The above changes in left ventricular geometry, papillary muscle position and annular dimensions interact to produce poor leaflet coaptation during systole, which is the final common pathway for Type IIIb ischemic MR.

Clinical Presentation

Type IIIb IMR can occur in an acute or chronic setting. "Acute post-infarction ischemic MR," without papillary muscle rupture, can be documented for many patients by physical examination, ventriculography or echocardiography. Moderate-to-severe MR is present in up to 13% of these patients (16, 17) . Acute severe type IIIb ischemic MR often presents with a sudden onset of shortness of breath and/or chest pain. In most patients this incident may be preceded by an acute episode of MI; however, in others (particularly diabetic patients) it may be silent. A minority of patients will present with symptoms of heart failure and/or low cardiac output.

Although the MR will resolve over time in some patients, it will persist in others leading to "chronic post-infarction ischemic" MR. In some patients, chronic IMR will first appear up to six weeks after the MI, as the infarcted left ventricle remodels. Risk factors for post-infarction IMR include advanced age, female gender, prior acute MI, large infarct size, recurrent ischemia, multi-vessel coronary artery disease and congestive heart failure (18). In patients with chronic IMR, two clinical scenarios are commonly encountered. Patients may present with moderate-to-severe MR, symptoms of congestive heart failure or worsening left ventricular function, and they are referred primarily for mitral valve surgery. The preoperative coronary angiogram shows significant multi-vessel coronary artery disease that may or may not have been symptomatic. These patients often have clear evidence of prior MI and at least moderate left ventricular dysfunction. Other patients present with symptomatic multi-vessel coronary artery disease and are referred for coronary artery bypass grafting (CABG) with a varying degree of MR on preoperative ventriculography or echocardiography. Acute coronary syndromes, or chronic stable angina is often the dominant presenting symptom in these patients. In addition they may present with symptoms of shortness of breath and/or congestive heart failure.

Diagnosis

Electrocardiogram. Patients often present with changes on their electrocardiogram (ECG). However, changes in favor of acute or remote MI are not observed in all patients (only half present with a diagnosis of acute MI, and in most series of chronic ischemic MR, a prior MI is noted in > 80% of patients). When the ECG changes become diagnostic, inferior wall infarctions are more common than anterior or lateral infarcts. Most patients are in sinus rhythm; however, following atrial enlargement, p-wave abnormalities and atrial fibrillation may occur in the chronic setting. Conduction abnormalities are uncommon in these patients.

Chest X-ray. In the acute setting, the chest X-ray may show evidence of pulmonary interstitial edema. With disease progression, enlargement of the cardiac silhouette (left atrial enlargement and ventricular dilatation) is a common finding.

2D-echocardiography/Doppler. This is an essential tool in determining the mechanism and severity of MR (19), and of left ventricular wall motion abnormalities and function. The severity of MR can be determined by semi-quantitative measurements using jet geometry and the area in multiple views. The severity of mitral regurgitation is graded on a scale from 1+ to 4+ (1+ trace, 2+ mild, 3+ moderate and 4+ severe MR with flow reversal in the pulmonary veins). More recently, quantitative Doppler methods have been developed allowing quantitative grading of MR (7, 20). This quantitative grading is based on the calculation of regurgitant volume and effective regurgitant orifice.

Transesophageal echocardiography (TEE). TEE can be used to determine the mechanism of MR; however, several studies have shown that TEE downgrades the severity of MR in patients with type I or IIIb dysfunction. The mechanism underlying this phenomenon is almost certainly the unloading effect of general anesthesia, which results in arterial and venous dilatation, decreasing afterload and preload, respectively (6, 21).

Cardiac MRI. MRI is a diagnostic tool that provides a precise definition of the mechanisms and severity of MR, as well as left ventricular function and viability.

Cardiac catheterization. Cardiac catheterization should be performed in all patients, in order to determine the extent and severity of coronary artery disease. Left ventriculography is useful in assessing left ventricular function, and segmental wall motion in selected patients.

Negative Impact of MR in Different Clinical Scenarios

There is a growing body of evidence on the negative impact of IMR on medium-term survival in patients with coronary artery disease. The poor prognosis of patients with ischemic MR has been documented in a variety of clinical settings (e.g., after MI, percutaneous transluminal coronary angioplasty [PTCA], and CABG) with three-year survival rates ranging from 50–75%, all depending on the severity of MR and other patient characteristics.

MR after Myocardial Infarction

Several studies have documented the strong impact of IMR on early and late survival after acute MI (16–18, 22, 23). Lamas et al. (22) studied 727 patients with acute MI from the SAVE trial (survival and ventricular enlargement). In this series, left ventriculograms were used to confirm MR after MI. The presence of MR was related to the risk of developing a cardiovascular event during 3.5 years of follow-up. MR was present in 141 patients (19.4%) (Fig. 2a). Even with similar ejection fractions, patients with MR had larger end-systolic and end-diastolic volumes and more spherical ventricles than patients without MR. They were also more likely to experience cardiovascular mortality (29% vs. 12%, p<0.001), severe heart failure (24% vs. 16%, p=0.0153), and the combined end-point of cardiovascular mortality, severe heart failure, or recurrent MI (47% vs. 29%, p<0.001). In this study, even mild MR at the time of presentation was an independent predictor of mortality (relative risk [RR] 2.0) (4). In another series, Lehman et al. (24) did a sub-group analysis of 206 patients in the TIMI trial (thrombolysis in MI). In addition, in this trial, patients underwent a left ventriculogram within 7 hours of onset of their MI, and MR was present in 13%. In this study also MR was shown to predict cardiovascular mortality by both univariate (RR 12.2, p<0.0001) and multivariate analyses (RR 7.5, p=0.0008).

Finally, Grigioni et al. (7) conducted a study of 303 patients with a q-wave MI who underwent transthoracic echocardiography. As opposed to the 2 previous series, the authors selected patients at distance from the initial MI (> 16 days). Two groups were matched and followed. At 5 years, overall mortality was 62% for patients with IMR, compared to 50% in patients without IMR (Fig. 2b).

MR after Percutaneous Coronary Intervention

Ellis et al. (25) studied survival in patients with coronary artery disease and MR who underwent percutaneous coronary intervention (PCI). Patients were classified into different groups by MR grade (by quantitative echo). They differed significantly in regard to demographics in all groups. The three-year survival ranged from 46–76% depending on the severity of MR. This data revealed that isolated PCI without addressing MR dramatically decreases survival at 3 years (Fig. 2c).

MR after Coronary Artery Bypass Grafting

Two large studies from the mid-1980s suggested that preoperative MR is an independent risk factor for late death in patients undergoing CABG. Hickey et al. (26) found that increasing MR severity had a progressively negative impact on survival, regardless of the treatment. Adler et al. (27) reported similar results from more than 2,000 patients undergoing primary CABG. Uncorrected MR was an independent risk factor for late death, with a relative risk of 1.5 for each grade of MR. A recent study by Harris et al. (28) comparing CABG with and without mitral valve surgery in patients with 2–3+ MR showed 5-year survival rates of 60% and improved survival in NYHA Class III–IV patients who underwent concomitant mitral valve surgery.

Surgical Indications

Moderate-to-Severe Ischemic MR

As previously mentioned, most patients presenting with moderate-to-severe MR have symptoms of congestive heart failure or worsening left ventricular function. In addition they often have severe 3-vessel coronary artery disease. Medical management of these patients is associated with poor clinical outcomes. It is well established that these patients should undergo combined mitral valve surgery and myocardial revascularization, provided that the operative mortality remains acceptable (29).

Mild-to-Moderate Ischemic MR

In this clinical scenario, patients are often referred for myocardial revascularization secondary to symptomatic coronary artery disease. The preoperative finding of mild-to-moderate type IIIb ischemic MR is often incidental.

Three recent studies have suggested that CABG alone does not completely correct IMR. Czer et al. (30) used intraoperative TEE to compare 25 patients who underwent CABG alone with

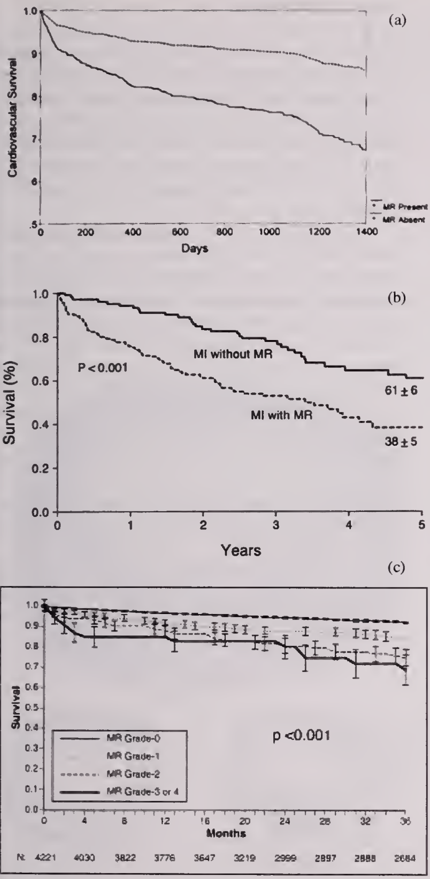

Fig 2: **(a)** Survival after acute myocardial infarction with early MR. Copied with permission from Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. Circulation 1997; 96(3):827–833 (22). **(b)** Survival after acute myocardial infarction—MR assessed late after MI (>16 days). Copied with permission from Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001; 103:1759–1764 (7). **(c)** Survival after PCI in patients with MR. Copied with permission from Ellis SG, Whitlow PL, Raymond RE, Schneider JP. Impact of mitral regurgitation on long-term survival after percutaneous coronary intervention. Am J Cardiol 2002; 89:315–318 (25).

24 patients who also underwent suture annuloplasty. In the CABG-alone group there was no change in the annular diameter, leaflet-to-annulus ratio or mean MR grade. This study was also limited by the fact that most patients had mild or trace MR. In addition, the hazards of interpreting MR severity by TEE without controlling loading conditions have been described above. Ryden et al. (31) reviewed 89 patients with 2+ MR undergoing CABG alone and reported that the MR was unchanged or worse in 38%. A study from Aklog et al. (6) from Brigham and Women's Hospital also concluded that CABG alone was not the optimal therapy for many patients with moderate IMR. In this study, 136 patients with moderate IMR underwent CABG alone. Among the 68 patients who underwent early postoperative transthoracic echocardiography, 40% showed no improvement and were left with moderate or severe (3–4+) residual MR. Approximately 50% of the patients had some improvement and were left with mild (2+) residual MR. Only a few remaining patients (< 10%), had significant improvement, with no more than trace (0–1+) residual MR. Thus, current literature seems to suggest that although CABG alone can decrease MR severity, especially in patients with mild IMR and poor left ventricular function, it has an inconsistent and relatively weak impact on moderate IMR, leaving many patients with 2+ or greater residual MR (32). Prifti et al. reviewed 99 patients with 2–3+ IMR and ejection fractions (EF) less than 30%, split evenly between CABG alone and CABG/mitral valve surgery (nearly all repairs) (33). Although the groups were comparable with regard to preoperative characteristic, concomitant mitral valve surgery led to improved EF, decreased left ventricular dimensions and improved three-year survival.

A few studies have examined whether CABG alone corrects IMR in a variety of settings. Christenson et al. reviewed 56 patients with severe left ventricular dysfunction (EF ≤ 25%) and varying degrees of MR by preoperative echocardiography who underwent CABG alone (34). They observed that 93% of patients had no more than trace (0–1+) MR and the remaining patients had mild (2+) MR on postoperative echocardiography. They concluded that "moderate co-existing MR seems to normalize after myocardial revascularization and should not be surgically corrected therefore at the primary operation." This study, however, has several limitations which make it difficult to interpret and do not justify this broad recommendation. Most important, only 7 patients (13%) in this study had moderate (3+) preoperative MR and more than 40% had trace (1+) MR. A similar study by Tolis et al. evaluated 49 patients with EF < 30% and "mild-to-moderate" MR who underwent CABG alone

(35). Mean MR grade decreased from 1.7 to 0.5, and the authors recommend CABG alone for this subgroup. These conclusions are limited by the fact that less than 10% of patients had 3+ MR and 40% had 1+.

Patients with mild-to-moderate IMR (2–3+) should undergo concomitant mitral valve repair at the same time as myocardial revascularization, unless preoperative risk factors suggest that the additional operative morbidity and mortality would be prohibitive (i.e., extensive mitral annular calcification, or strong indication for off-pump CABG in patients with heavily diseased aortas).

Surgical Management

Perioperative Considerations

Standard techniques of monitoring (e.g., arterial line, central venous access, Foley catheter) are used in patients undergoing combined mitral valve repair and CABG. A Swan-Ganz catheter should be inserted in every patient. A transesophageal echocardiogram (TEE) should be performed (36). TEE is a key element for determining the mechanism of MR, assessing LV function and quality of repair, and de-airing of the cardiac cavities at the completion of the procedure. Because afterload reduction secondary to general anesthesia downgrades the degree of MR, TEE is not used to assess MR severity. An epiaortic scan of the ascending aorta is recommended, to rule out the presence of atherosclerotic lesion prior to arterial cannulation.

Surgical Approaches, Cardiopulmonary Bypass, and Myocardial Protection

Median sternotomy is the surgical approach of choice for patients undergoing combined mitral valve repair and CABG, and should be used in the reoperative setting as well. However, in rarer cases, a right anterolateral thoracotomy may be used for selected patients referred for isolated ischemic MR with prior CABG and patent grafts, particularly internal thoracic arteries. Cardiopulmonary bypass is instituted between the ascending thoracic aorta and both venae cavae. Intermittent antegrade, or combined antegrade and retrograde cardioplegia with high-potassium-content cold blood, is used for myocardial protection. Further myocardial protection can be obtained by moderate systemic hypothermia (between 28 and 30°C) and local hypothermia with topical ice. Careful de-airing at the end of the procedure is essential.

Mitral Valve Repair

Following completion of coronary bypass grafting, the perfect exposure of the mitral valve is essential before undertaking mitral valve repair. The most commonly used approach is the interatrial approach through Sondergaard's groove. Mitral valve repair is the procedure of choice for correction of type IIIb ischemic mitral regurgitation.

The goals of valve repair include preserving leaflet mobility and restoring a large surface of coaptation by reducing the septo-lateral dimension with a remodeling annuloplasty. The valvular apparatus is examined with a nerve hook in order to assess the precise mechanism of MR (37). As previously mentioned, it is posterior leaflet restriction due to posterior papillary muscle displacement, affecting P2 and P3 with associated annular dilatation, which is most commonly present (Fig. 3).

Undersized Remodeling Ring Annuloplasty for Type IIIb Ischemic MR

Remodeling annuloplasty using a prosthetic undersized ring is the technique of choice in type IIIb dysfunction (29). Once sutures are placed around the annulus, standard ring sizers are used to

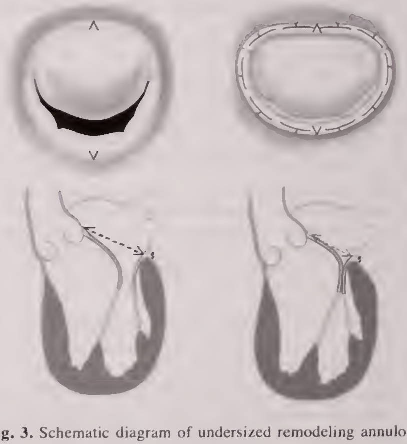

Fig. 3. Schematic diagram of undersized remodeling annuloplasty. **Left:** In patients with type IIIb MR there is a significant restriction of the posterior leaflet and an associated annular dilatation (AP diameter > transverse diameter). **Right:** Undersized remodeling prosthetic annuloplasty restores a large surface of coaptation with the physiological ratio of the mitral annulus, while preserving maximum orifice area.

select the appropriate ring, then the ring is selected and the interrupted sutures are passed through it. When completed, a saline test is used to confirm the line of coaptation along the margin of the leaflets. Nearly the entire orifice is occupied by the anterior leaflet, allowing the entire restricted posterior leaflet to increase the surface of coaptation (Fig. 4).

Surgical Results

Operative Mortality

Concomitant mitral valve surgery/CABG has a mortality rate of over 10%. Several authors have demonstrated that early and late outcomes of combined mitral valve and CABG depend strongly on the underlying etiology, to the extent that it can be determined in retrospective analyses, with significantly worse outcome in ischemic disease (8, 9, 38). Although the reported operative mortality for mitral valve replacement at the time of CABG has remained relatively high (4, 8, 39–41), the outcomes for mitral valve repair appear to be improving over time (4, 8, 40, 41), with most recent series reporting operative mortalities well under 10%. For 2002, the STS database reported an 8% operative mortality for mitral valve repair/CABG (down from 12% in 1993) and 11.5% mortality for mitral valve replacement/CABG (down from 17% in 1993) (42). Filsoufi et al. (43) reviewed early outcomes following CABG and mitral annuloplasty for moderate (3+) IMR and found that operative mortality had decreased from 14% to 3.7% during the 1990s (29). The latter rate was not dramatically different from the 2.9% mortality reported previously in an unmatched but contemporaneous group of patients undergoing CABG alone for moderate IMR (6).

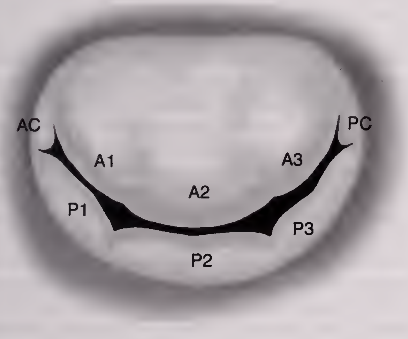

Fig. 4. Segmental description of the valvular tissue. The mitral valve is divided into 8 segments: anterolateral and posteromedial commissures (AC, PC), and posterior and anterior leaflets, which are divided into P1, P2, P3 and A1, A2, A3 segments respectively.

Late Outcomes

Multiple reports over the past twenty years suggest that late survival in patients with IMR undergoing mitral valve surgery is suboptimal and significantly worse than in those with degenerative or rheumatic mitral valve disease (12, 28, 30, 40, 43–45). Medium-term (3–5 year) survival in these studies ranged from 50–80%, depending on the risk profile. Two recent studies have sought to directly compare outcomes following CABG alone with those following CABG/mitral valve surgery.

Prifti et al. reviewed 99 patients with 2–3+ ischemic MR and EF < 30, split evenly between CABG alone and CABG/mitral valve surgery (nearly all repairs) (33). In this series, concomitant mitral valve surgery led to improved ejection fraction, decreased left ventricular dimensions and improved three-year survival. Harris et al. (28) reviewed 196 patients with 2–3+ IMR and an average ejection fraction of 39% (142 CABG alone, 44 with concomitant mitral valve surgeries—mostly repairs). Those undergoing mitral valve surgery had a higher operative mortality (21% vs. 9%), but overall long-term survival was no different. In the subgroup of patients with NYHA Class III–IV heart failure, however, concomitant mitral valve surgery provided a significant survival advantage. An important secondary finding in this study was an approximately 50% incidence of 2+ or greater residual MR in patients undergoing mitral valve repair, a result which the authors acknowledge is suboptimal. Di Donato et al. (32) reviewed 60 patients with moderate IMR undergoing CABG alone (n=30) and CABG/annuloplasty (n=30) from 1998–2001. All patients underwent follow-up echocardiography at 12 and 36 months postoperative. At follow-up, it appeared that the CABG/annuloplasty patients had a lower NYHA classification, fewer signs and symptoms of congestive heart failure, and better echocardiographic parameters (smaller LV volume, increased ejection fraction, and lower pulmonary artery pressures). In this series, the preoperative annular size was seen to be a risk factor for postoperative heart failure events. The authors conclude that the combined approach for patients with moderate MR leads to a better clinical status and better hemodynamic profile.

Overall, these data suggest that concomitant mitral valve surgery might improve late outcomes for patients with IMR, especially for those with heart failure, and if it can be performed with little additional operative risk and a low incidence of residual MR.

Residual Mitral Regurgitation

Although the routine use of a remodeling annuloplasty and more aggressive downsizing will probably decrease the incidence of residual MR after CABG/annuloplasty, there is a small group of patients for whom a classical undersized remodeling annuloplasty may not sufficiently correct MR.

Aklog et al. (6) recently reported on 288 patients with Carpentier type I or IIIB IMR who underwent CABG/annuloplasty. A complete remodeling, semi-rigid ring (Carpentier-Edwards Physio, Edwards Lifescience, Irvine, CA) was used in 92 patients and a partial, restrictive, flexible band (Cosgrove-Edwards, Edwards Lifescience, Irvine, CA) in 196. Patients who received a Carpentier ring had less residual MR ≥ 2+ (14% vs. 21%, p=0.10). The mechanism of residual MR was impaired leaflet coaptation as a result of isolated annular dilatation (type I) and/or leaflet restriction (type IIIb). One possible explanation for residual MR after CABG/annuloplasty is inadequate downsizing. The anteroposterior dimension must be aggressively reduced to bring the restricted posterior leaflet close enough to the anterior leaflet to allow adequate coaptation. Inadequate downsizing can lead to inadequate coaptation and residual MR.

Furthermore, a recent clinical study from the Cleveland Clinic has provided anatomical and morphological descriptions of type IIIb IMR, which may also be a potential explanation for residual MR after undersized remodeling annuloplasty. In this study, three-dimensional echocardiography was used to further refine analysis of leaflet restriction (type IIIb) in ischemic vs. dilated cardiomyopathy (46). The authors observed a significant difference in mitral valve deformation between the two patient groups. The pattern of mitral valve deformation from the posteromedial to the anterolateral commissure was asymmetrical in the ischemic group, while it was symmetrical in patients with dilated cardiomyopathy. These differences in mitral valve geometry underscore the fact that in patients with ischemic cardiomyopathy, the P2 and P3 segments are the most restricted segments, causing an asymmetrical mitral orifice. These asymmetrical morphological changes may explain why the implantation of a symmetrical, undersized prosthetic ring insufficiently reduces the septo-lateral dimension in some patients with type IIIb IMR, and may be the main cause of residual MR after valve repair (6, 9, 29).

New Developments: Carpentier-McCarthy-Adams Etlogix Ring

In an attempt to address the above-mentioned issues (inadequate undersizing, marked P2–P3 restriction relative to P1) and to potentially reduce the incidence of residual MR, a new remodeling annuloplasty ring was developed in collaboration with the Department of Cardiothoracic Surgery at Mount Sinai Medical Center, New York. This new prosthetic ring combines the principles of undersizing, while addressing the specific asymmetric deformation observed in type IIIb IMR (Fig. 5). This new design leads to increased leaflet coaptation due to the reduced anteroposterior (AP) dimension. In addition, the asymmetric 3-D design with reduced P2–P3 curvature allows for a better accommodation of tethered P2–P3 segments (Fig. 5).

The Carpentier-McCarthy-Adams Etlogix ring was first implanted at Mount Sinai Medical Center in December 2003, shortly after Food and Drug Administration (FDA) approval. Fifteen patients (14 male and 1 female, mean age of 66 years) presented with greater than 3+ MR. The mean ejection fraction was 31% (10–57), and all patients were in NYHA Classes III and IV. They underwent successful mitral valve repair with this new prosthetic ring (mean size 28 mm). Concomitant procedures included CABG, left-atrial maze, tricuspid valve repair and patent foramen ovale closure. Expected operative mortality calculated by Euroscore for this cohort was 19% (4–47). However, the ob-

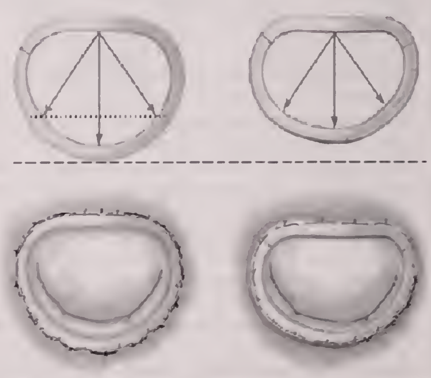

Fig. 5. Carpentier-McCarthy-Adams Etlogix Ring (Edwards Lifescience, Irvine, CA). This image shows a symmetrical Carpentier-Edwards Physio Ring (on the left), and the new asymmetrical Carpentier-McCarthy-Adams Ring (on the right). The new ring is already undersized, and has a 14% reduction in the postero-medial dimension (P2–P3 segments).

served operative mortality was 0%. Pre-discharge transthoracic echocardiography for all patients showed a significant reduction in mean MR grade (from 3.5 to 0.6, p>0.05).

Type II Ischemic MR

In this functional type of MR, the motion of one or two leaflets is excessive and the free edge of the leaflet overrides the plane of the orifice during systole. Leaflet prolapse results from partial or complete rupture of one papillary muscle or from papillary muscle elongation or, more rarely, from chordal rupture.

Papillary muscle rupture is a rare mechanical complication of MI; without early diagnosis and expeditious medical and surgical management, it has a high mortality rate. This complication occurs in 1–5% of patients who die following MI (47). Papillary muscle rupture can occur during the acute phase of MI; however, most patients present within 2–7 days after MI (48). Complete papillary muscle rupture occurs in 30% of patients and results in bi-leaflet prolapse with severe mitral regurgitation. However, partial rupture of one papillary muscle involving one or more heads remains the most common lesion in patients with type II IMR. Myocardial infarction often involves a limited area of the myocardium, which may explain the relatively well-preserved left ventricular function in most patients (3). Papillary muscle elongation results from fibrotic transformation of papillary muscle following MI. The elongation of papillary muscle causes leaflet prolapse, resulting in MR. Most patients present with chronic IMR and do not require emergency surgical treatment.

Patients with papillary muscle rupture present with sudden development of congestive heart failure and cardiogenic shock. This rapid deterioration of the clinical condition in previously stable patients should suggest the diagnosis of a mechanical complication of MI. Clinically, it remains very difficult to distinguish between these two entities, despite differences in the characteristics of the murmurs. Another common differential diagnosis is extensive MI with cardiogenic shock associated with varying degrees of ischemic mitral regurgitation without papillary muscle rupture. Other preoperative examinations, including two-dimensional transthoracic echocardiography, TEE with Doppler and cardiac catheterization, are crucial for making the accurate diagnosis of IMR due to papillary muscle rupture and evaluating left ventricular function and the severity of coronary artery disease. The principal goal of preoperative medical management is hemodynamic stabilization (preservation of cardiac output and arterial pressure to maintain peripheral organ perfusion as well as the preservation of coronary blood flow). This is best achieved with the use of inotropic agents and prompt insertion of intra-aortic balloon pump (3). However, this stabilization phase should not delay surgical intervention in these critically ill patients. Based on the preoperative investigations, the surgical procedure should combine the correction of mitral regurgitation and myocardial revascularization.

Chordal-sparing mitral valve replacement remains the procedure of choice for most patients. This technique preserves postoperative left ventricular function, contributing to improved long-term survival of these patients (49–52). However, in selected patients, mitral valve repair with papillary muscle shortening or papillary muscle reimplantation can be done using Carpentier's techniques of valve repair (53).

Operative mortality has traditionally been high. In a recent publication, Tavakoli et al. (3) reported a consecutive series of 21 patients who underwent mitral valve surgery (replacement, n=19; repair, n=2) and CABG (52% were urgent/emergent). Operative mortality was 19%; the principal postoperative complications were stroke (6%) and renal failure requiring hemodialysis (18%). In this series actuarial survival at 1, 5, and 10 years was 81, 68 and 56%, respectively. The survival seen in this series compares well to that in a similar study from the Cleveland clinic (4), which demonstrates a survival rate of 55% after 7 years. Even though early mortality is high in the acute setting, aggressive surgical treatment does improve long-term outcome, as this allows the correction of an acute hemodynamic compromise (54–56).

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An Unusual Localization of Snakebite Treated without Antivenin:

Case Report

Salim Satar, M.D.[1], Ozgur Karcioglu, M.D.[2], and Ahmet Sebe, M.D.[1]

Abstract

Snakebite is one of the commonest causes of morbidity and mortality in tropical regions. This paper focuses on the medical treatment of a patient who had been bitten by a snake on the vertex of his head. It was a severe envenomation with ensuing marked edema associated with coagulation abnormalities. Although the antivenin was extensively sought in various medical centers, it was unavailable. We observed and treated the patient, with special regard to his hematological findings and potential complications. Specifically, tetanus prophylaxis and intravenous fluids were administered, and the wound was cleaned and dressed. Fresh frozen plasma was also administered. The patient responded well, and was discharged on the fourth day of his admission, without any sequelae.

Key Words: Antivenom, antivenin, envenomation, snake, snakebite, treatment.

Introduction

Treatment with antivenin derived from polyvalent snake venom is considered the standard of care in Turkey for the treatment of moderate or severe snake envenomation. A number of reports indicate that most poisonous snakes living in Turkey belong to the *Viperidea* and *Elapidea* families, and that venoms of these snakes can affect the blood coagulation mechanism of their prey (1). Viper venom antivenin is prepared from the purified plasma of healthy horses that have been immunized against the most dangerous vipers. The efficacy of polyvalent antivenin has been demonstrated in animal studies, but there is still controversy regarding its appropriate use in humans (2). Many authors have published antivenin-dosing regimens for the treatment of snake envenomation (3). Nevertheless, many physicians delay giving treatment, or they give too small a dose of antivenin, for fear of the dangerous side effects (2).

In this article we report a severe envenomation in a patient who was treated successfully without antivenin in an emergency department.

Case

A fifteen-year-old male patient was admitted to the emergency department three hours after he had been bitten on the vertex of his head by a snake while he was drinking water from a stream. Physical examination revealed remarkable nonpitting edema on his face and two adjacent fang marks on the vertex of his head. His relatives also had produced a laceration with a sharp knife near the fang marks while giving him "traditional" first aid. The laceration was only on the surface of his scalp.

His vital signs were: blood pressure 100/60 mm Hg, pulse rate 112bpm, respiratory rate 22, and temperature 36.3°C. He was lethargic. There was a marked edema including partial ecchymotic areas from his face through his neck (Fig. 1). His laboratory findings were as follows: blood urea nitrogen 18 mg/dL, creatinine 0.7 mg/dL, glucose 192 mg/dL, sodium 137 mmol/L, potassium 4.5 mmol/L, chloride 105 mmol/L, total bilirubin 0.9

From the [1]Department of Emergency School of Medicine, Çukurova University, Adana, Turkey and [2]Department of Emergency, School of Medicine, Dokuz Eylul University, Izmir, Turkey.

Address all correspondence to Salim Satar, M.D., Çukurova University, Faculty of Medicine, Emergency Department, 01330, Balcalı/Adana, Turkey; e-mail: ssatar@cu.edu.tr

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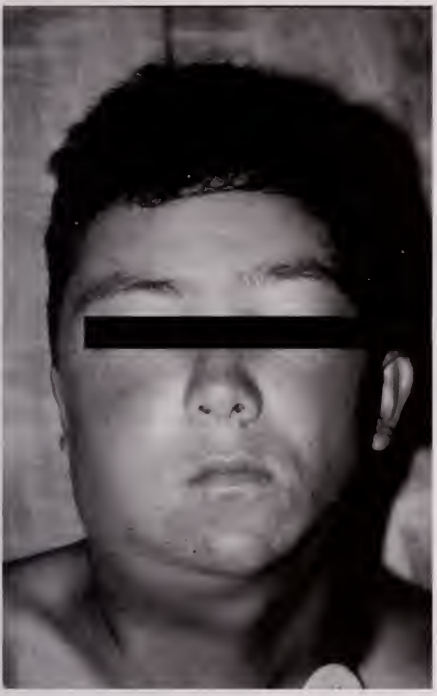

Fig. 1. Photograph of the patient on admission.

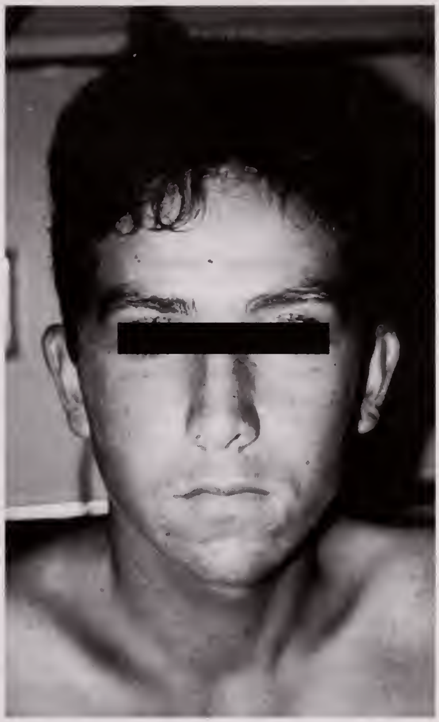

Fig. 2. Photograph of the patient after treatment.

mg/dL, indirect bilirubin 0.2 mg/dL, aspartate aminotransferase 48 u/L, alanine aminotransferase 34 u/L, lactic dehydrogenase 965 u/L, amylase 48 u/L, hemoglobin 14.9 g/dL, hematocrit 44.3%, white blood cells 20,400 uL, erythrocytes 5,500,000 uL, and platelets 94,000 uL. Coagulation studies disclosed prothrombin time as 20 sec, international normalized ratio 2.8, fibrinogen 130 mg/dL, and fibrin-degrading products > 500 ng/dL. The patient's arterial blood gas analyses were normal. Urinalysis revealed minimal hematuria. Chest x-ray and electrocardiogram revealed no pathology. With these findings, he was hospitalized and diagnosed as having a grade three snakebite. Although we decided to administer antivenin, the agent was not available locally. Tetanus prophylaxis and intravenous fluids were administered, and the wound was treated with local cleansing and dressing. We administered fresh frozen plasma because of his coagulation abnormalities. His hematological parameters were closely observed. After 12 hours, coagulation tests were normal. On the second day, his edema subsided; on the third day, local wound findings and edema were completely healed (Fig. 2). He was discharged on the fourth day of hospitalization.

Discussion

Although uncommon, venomous snakebites are potentially lethal emergencies. Venomous snakes can be classified as having either hematotoxic or neurotoxic venom (4). Clinical effects of snakebites range from mild local reactions to life-threatening systemic reactions, depending on the species and size of snake involved; the location of the bite; the volume of venom injected; and the age, size and health of the victim (5). Patients with snakebites must be admitted and treated as true emergency cases, and the mainstay of hospital treatment for venomous snakebite is antivenin (6). The general indications for the administration of antivenin are progression of the injury, worsening local injury, and clinically important coagulation abnormalities or systemic effects (7). Of the 53 species of snakes native to Turkey, 2 species are dangerous. These species belong to the *Viperidea* and *Elapidea* families, which are also called pit vipers (1, 8). Pit viper snake venoms are hematotoxic. Biochemically, the venom consists of proteins, polypeptides and enzymes that cause necrosis and hemolysis. Most pit viper bites induce pain within five minutes, and local swelling is marked soon after. Symptoms of hematologic involvement and systemic reactions (including a syndrome similar to disseminated intravascular coagulation, acute renal failure, hypovolemic shock and death) may recur (7). These patients must receive antivenin, because no other treatment can reverse the venom's effect (9).

The emergency management of snakebites in our department consists of cleaning the wounds, administering tetanus toxoid or immunoglobulin for under- or non-immunized patients, marking the leading edge of the swelling and recording the time of observation, and measuring the circumference of the affected extremity every 30 minutes. If there is no proximal progression of local injury on the extremity and no coagulopathy after 12 hours of clinical observation and serial laboratory examination, the patient can be discharged home with follow-up instructions. These instructions strictly stress that the patient must return to the physician if there is any increase in pain, redness or swelling; faintness; shortness of breath; or diaphoresis. Antivenin is administered to patients with moderate or severe envenomation, unstable patients (i.e., those with hypotension, severe coagulopathy, respiratory distress), and when there is a progression in the wound or hematological parameter during observation. We use horse-derived antivenin in our department. The dosage is 2–4 vials for mild envenomation, 5–9 vials for moderate cases and 10–15 vials for severe ones. If new manifestations appear, we administer an additional 1–5 vials titrated to effect.

The presumption of efficacy for antivenin is based on animal studies, several retrospective studies, and numerous case reports (10). However, the use of antivenins has been questioned because of a hypothetical unfavorable risk/benefit ratio (11). The primary risks associated with the use of antivenin are anaphylaxis and serum sickness (10). In retrospective studies, rates for acute allergic reactions (including hypotension and anaphylaxis) from antivenin administration range from 23–56%, with even higher rates for delayed serum sickness (10). However, neither the risks nor the benefits have been studied prospectively (10).

The efficacy and relative safety of antivenins have been demonstrated in randomized trials (12), but most physicians believe it is dangerous to treat snakebites using polyvalent antivenin because of the high risk of anaphylaxis (2, 13). Although the actual incidence of side effects of snake antivenin is unknown, in one review of 26 patients receiving antivenin, type 1 hypersensitivity occurred in 6 patients (23%) and type 3 hypersensitivity occurred in 13 (50%). This study suggested that the incidence of serum sickness was related to dose in 83% of patients given more than 8 vials of antivenin (14). The findings of that study, together with other reports, have understandably led to concern about using polyvalent antivenin therapy and a reluctance by clinicians to administer this potentially beneficial treatment (14, 15). In another study, Dart et al. summarized eight studies designed to monitor acute and delayed reactions to the antivenin (10). In this study, 78% of 592 patients were treated with antivenin. In the treatment group, 79 patients experienced acute reactions to the antivenin (mostly urticaria) and 13 of these experienced hypotension; no deaths attributed to anaphylaxis were reported. Even though the authors themselves were aware of three deaths from anaphylaxis, they noted that no such deaths had actually been published in the medical literature (10). The study by Offerman et al., however, suggests that fears about the antivenin are unfounded (2). In this retrospective study of 73 patients, of the 12 patients who experienced acute reactions to the antivenin, the reactions of 11 consisted solely of urticaria; only one patient developed hypotension, which required a short course of epinephrine. They noted that anaphylactic shock is extremely rare in the treatment of snakebites with antivenin (2).

Our patient did not receive antivenin because it was not available in our emergency department at the moment it was needed. The management of the patient consisted of close monitoring and supportive care. Coagulation abnormalities were treated with fresh frozen plasma. Monitoring trends in the coagulation profile is one objective way of assessing the seriousness of envenomation and the response to antivenin therapy (7). The decision to administer blood products should be based primarily on clinical condition, trend of clotting parameters and other standardized criteria for the treatment of coagulopathies (16). Criteria for the use of blood products appear to be quite arbitrary in clinical practice. It is recommended that blood products be used only if antivenin fails to take effect and that component therapy be used for specific conditions (7).

In conclusion, the omission of antivenin treatment did not lead to adverse consequences in the present case with moderate hematological abnormalities associated with deliberate snake envenoming. Although this finding could be attributed to "regional" variations, the general belief that the mainstay of treatment of snake envenoming should include antivenin deserves to be reconsidered. There still remain many questions about the treatment of envenoming. Finally, the role of close patient monitoring and good supportive care cannot be overemphasized.

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Bilateral Synchronous Breast Cancer in a Male

Peter B. Kahla, M.D.[1], Sebastiano Cassaro, M.D.[1], Felix G. Vladimir, M.D.[1], Michael G. Wayne, D.O.[1], and Angelo Cammarata, M.D.[2]

Abstract

Breast cancer in males is rare, accounting for less than 1% of all cases. Bilateral male breast cancer is reported to occur in fewer than 2% of all the diagnosed cases of male breast cancer, and synchronous tumors are exceedingly rare. The authors report a case of male breast cancer that is bilateral and synchronous, and review the literature on male breast cancer.

Key Words: Breast cancer, male, bilateral, synchronous, prognosis, review.

Case Report

A 71-YEAR-OLD AFRICAN-AMERICAN MALE accidentally discovered a mass in his left breast. Family history was negative for breast cancer and his medical history was unremarkable. There was no history of alcohol use and he was not taking any medications. On physical examination of the left breast a hard, poorly defined mass with a diameter of 2 cm was noted. It was fixed to the overlying nipple-areola complex and caused nipple retraction. Examination of the right breast revealed a hard, fixed nodule in the retroareolar region, measuring about 1.5 cm in diameter. Both axillae and supraclavicular fossae were free of palpable lymphadenopathy, and there was no evidence of abdominal organomegaly. Laboratory values were within normal limits. Chest X-ray was normal. Mammography was consistent with a dominant 2 x 2 cm left retroareolar mass with spiculated borders, breast imaging - reporting and data system (BI-RADS) category 4. No discrete mass was mammographically identifiable on the right.

Excisional biopsies of both lesions were positive for carcinoma. The left-sided tumor proved to be a 2 cm infiltrating ductal cell carcinoma (see Figs. 1 and 2). The right breast lesion revealed a 1.2 cm moderately differentiated intraductal carcinoma (see Figs. 3 and 4). Hormonal receptors were strongly positive on both sides. To achieve adequate margins around these relatively large lesions, the patient underwent bilateral modified radical mastectomies. The sentinel node technique was not used, because the masses were moderately differentiated and there was a strong suspicion that the nodes would be involved. On final pathology, however, the lymph nodes in both axillae were free of metastasis. The patient's postoperative course was uneventful. Subsequently, he received six

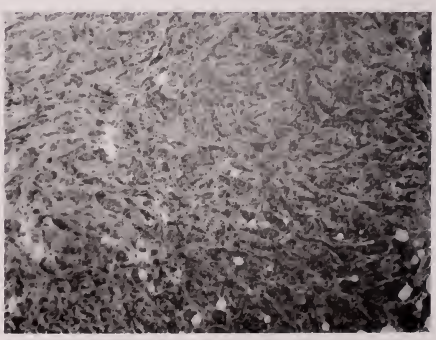

Fig 1. Left breast: infiltrating ductal carcinoma (H&E stain × 100).

From the [1]Department of Surgery, Cabrini Medical Center, Mount Sinai School of Medicine, NY, and the [2]Breast Surgery Service, Cabrini Medical Center, New York, NY.

Address all correspondence to Sebastiano Cassaro, M.D., Cabrini Medical Center, Department of Surgery, D-309, 227 East 19th Street, New York, NY 10003; e-mail: scassaro@cabrininy.org

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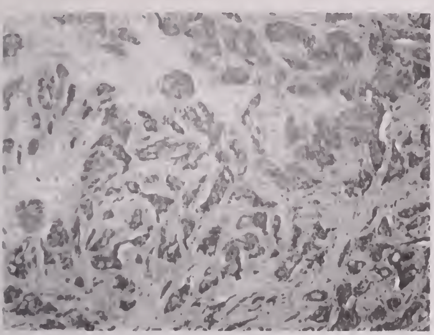

Fig 2. Left breast, higher magnification: infiltrating ductal carcinoma (H&E stain × 200).

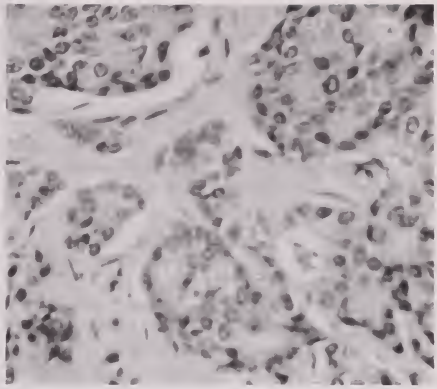

Fig 4. Right breast, higher magnification: intraductal carcinoma (H&E stain × 400).

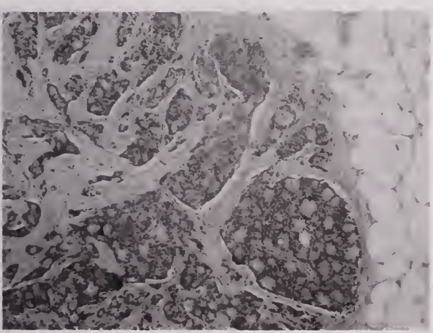

Fig 3. Right breast: invasive intraductal carcinoma (H&E stain × 100).

months of CMF (cyclophosphamide, methotrexate, 5-florouracil), followed by tamoxifen. After 17 months of follow-up, the patient was still alive, with no evidence of recurrence.

Discussion

Breast cancer occurs infrequently in males: of the 212,600 new cases projected to be diagnosed in the U.S. during 2003, only 1,300, or less than 1%, were expected to affect men. For the same year, deaths from the disease were forecasted at 40,200 women and 400 men (1). Five-year survival rates for the period 1995–2000, however, remained lower for men (81.1%) than for women (87.7%) (2). The mean age of detection in males is between 60 and 66 (3), which is 6–10 years later than the average age for women.

Crichlow reported that synchronous bilateral cancer occurs in 1.4% of male cases (4). Studies have shown that bilateral breast cancer has a worse prognosis than unilateral breast cancer, with a higher rate of distant metastasis and a lower disease-free survival rate (5).

According to Warren and Gates, three criteria must be satisfied in order to classify two or more tumors as synchronous primary malignancies (6):

1. Each tumor must be malignant
2. Each tumor must be distinct, i.e., different in its histological type from the other
3. Neither tumor can originate with metastasis from another tumor

The etiology of breast cancer in males remains elusive, but several predisposing factors have been proposed:

1. Feminization resulting from hyperestrogenism, either genetic or exogenous (7)
2. Hyperestrogenism secondary to liver dysfunction, as seen in patients with cirrhosis, schistosomiasis, or malnutrition (4)
3. Suppression of testicular function, as in Klinefelter's syndrome (8), or as a sequel of orchitis, testicular injury, undescended testis, or occupational exposure to heat or toxic chemicals (9)
4. Gynecomastia (10)
5. Exposure to ionizing radiations (10)
6. Exposure to electromagnetic fields for more than 30 years (11)

7. Hyperprolactinemia secondary to head trauma or to ingestion of prolactin-elevating drugs (12)
8. Race, religion, and geography (13)

Familial risk is reported in a few clusters of male breast cancers, but the information remains limited. With the recent availability of BRCA1 and BRCA2 genetic testing, it has been found that 10% of men with a mutation in the BRCA2 gene develop breast cancer, a risk not observed in men with a BRCA1 mutation. Similar risks are found in women with BRCA2 (14).

The discovery linking the genes BRCA1 and 2 to familial breast cancer is beginning to play an important role in the clinical practice of geneticists and physicians. The availability of genetic tests for BRCA gene mutations has prompted cancer geneticists to provide information about genetic risk, and to assess many women with a personal or family history of breast or ovarian cancer, informing them of preventive measures. These measures consist mainly of breast self-examination, mammography screening, chemoprevention, and prophylactic surgery (mastectomy, oophorectomy) (15).

The most common finding in male breast cancer is a mass. There is no screening program designed for males, so their cancers are usually diagnosed at a later stage than those found in women. The masses must be differentiated from gynecomastia. The cancerous masses are typically unilateral, hard, non-tender and poorly defined, and they are located beneath or adjacent to the nipple areola complex. The masses seen in patients with gynecomastia are usually bilateral, tender, well defined and just beneath the nipple. Other frequent symptoms of male breast cancer are nipple retraction, edema, ulceration and nipple discharge (4). Bloody nipple discharge is associated with 75% of the cancers (16). Other signs may involve skin changes such as ulceration, edema, erythema, retraction or presence of nodules and axillary lymphadenopathy (16). Mammographically, the primary characteristic is the presence of a mass, usually lobulated, spiculated, or ill defined, characteristically eccentric to the nipple. Micro-calcifications can occur, usually in the presence of a mass.

Because the natural course of breast cancer appears to be similar in both sexes, its treatment is generally similar, but there are a few differences worth discussing.

In men, modified radical mastectomy is the procedure of choice. Lumpectomy with postoperative radiation is not usually possible for male breast cancer, because the cancers are usually adherent to the pectoralis fascia and the male breast is small, thus preventing adequate margins. In cases where the cancer extends to the pectoralis muscle, part or all of the muscle should be resected to obtain local regional control. In cases of small lesions with no palpable axillary nodes, the sentinel node procedure can be used (5). Post-mastectomy radiation is reserved for patients with positive lymph nodes or cancer infiltrating the pectoralis muscle (17).

In the absence of sufficiently reliable clinical data and in line with the hypothesis that breast cancer in men and women should behave similarly, adjuvant systemic treatment should follow the guidelines outlined for women. Patients found to have positive lymph nodes should receive CMF or CAF (cyclophosphamide, Adriamycin, 5-florouracil), followed by tamoxifen if the hormone receptors are reported to be positive (18). Because most male breast cancers are hormone-receptor positive, hormonal therapy is a mainstay of treatment, and tamoxifen is the first-line choice. Many men, however, develop side effects that force them to abandon tamoxifen administration (19). Since the incidence of male breast cancer is low, there have not been any studies evaluating the role of tamoxifen as prophylaxis in high-risk male patients (20).

Males with breast cancer exhibiting the same TNM (primary tumor, regional lymph nodes, and distant metastasis) stage and receiving the same treatment as a woman have essentially the same prognosis (13). The belief that male breast cancer has a poorer outlook is based on its tendency to be diagnosed at a later and more advanced stage. This delay in diagnosis is a consequence of the very limited public awareness and the absence of screening protocols for male breast cancer. Male breast cancer does, however, occur and patients must become aware of its existence and the importance of seeking surgical attention and evaluation for any lump in their breasts.

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Loss of Vision and Renal Function in a Patient with Miliary Tuberculosis

Mustafa Balal, M.D., Saime Paydas, M.D., Neslihan Seyrek, and Ibrahim Karayaylali

Abstract

Introduction: Visual loss is a rare complication of tuberculosis; it can be related to anti-tuberculous drugs or to the infection itself. For the treatment of visual loss, differential diagnosis is important between infection and adverse effect of anti-tuberculous drugs.
Case: A 48-year-old male patient with a history of tuberculosis and visual loss during anti-tuberculous drug therapy was admitted to our hospital. Anti-tuberculous drugs had been stopped on the 2nd day of therapy due to development of optic neuritis secondary to ethambutol administration at another hospital. He had miliary tuberculosis, renal failure requiring dialysis and visual disturbances. Anti-tuberculous drugs, including ethambutol, were initiated at our clinic because the period between the ethambutol therapy and visual loss was too short and the dose of ethambutol was not very high. Computed brain tomography was normal. Fundoscopic examination revealed only hypertensive retinopathy. Our diagnosis was tuberculosis-related visual loss, which could be due to neuroretinitis, intraocular tuberculosis or chiasmal tuberculoma. In addition, ethambutol rarely causes visual loss during the early period or when given at lower doses. In our case no complications developed from the treatment and the patient's visual loss and renal function improved. At his last visit, 12 months later, his vision had improved and his serum creatinine was lower, at 2.2 mg/dL.
Conclusion: With anti-tuberculous treatment, renal functions and visual disturbances were improved in a patient with miliary tuberculosis. During the anti-tuberculous therapy, visual loss can be related to ethambutol toxicity or the tuberculosis infection itself. Differential diagnosis is very important and anti-tuberculous drugs must be continued if the diagnosis is tuberculosis.
Key Words: Anti-tuberculosis drug toxicity, visual loss, tuberculosis, renal failure.

THE FORM OF DISSEMINATED TUBERCULOSIS that is associated with primary infection or reactivation of tuberculosis is often seen in children and immunocompromised individuals, and it causes multi-organ failure if it cannot be controlled. Sudden blindness is a rare complication during active tuberculosis (1). We report a case of disseminated tuberculosis associated with acute renal failure and loss of vision.

Case

A 48-year-old man had previously been admitted to another hospital because of productive cough and dyspnea. The patient had a history of abdominal pain, nausea, vomiting, fever, night sweat and weight loss of 15 kg over 5 months. On physical examination, bilateral supraclavicular and axillary lymph nodes were found; pathological diagnosis indicated hyperplastic lymph nodes. This patient had acute renal failure and required hemodialysis 8 times. Anti-tuberculous treatment included ethambutol (15 mg/kg/day), isoniazid (300 mg/day), rifampicin (600 mg/day) and pyrazinamide (15 mg/kg/day). Two days later, sudden blindness occurred. Due to the possibility of optic neuritis from ethambutol, this drug was stopped. Prednisolone (100 mg/day) and pyridoxine (20 mg/day) were started. His vision improved one day later and he was transferred to our nephrology clinic. On admission, his temperature was 37.8°C, pulse 92 beats/min, and blood pressure 110/80 mm Hg. Hypertensive retinopathy was found on fundoscopic examination. Axillary and supraclavicular lymph nodes of 1×1 cm and 1×1.5 cm, respectively, were detected. Laboratory investigation showed a blood leukocyte count of 9,200/mm^3, hematocrit 31.8%, hemoglobin 11.02 g/dL, platelets 390,000/mm^3, erythrocyte sedimentation

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From the Department of Nephrology, Cukurova University Faculty of Medicine, Adana/Turkey.

Address all correspondence to Saime Paydas, M.D., Department of Nephrology, Cukurova University Faculty of Medicine, 01330 Adana/Turkey.

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rate 64 mm/hour, serum glucose 78 mg/dL, blood urea nitrogen (BUN) 140 mg/dL, creatinine 10.8 mg/dL, aspartate transaminase (AST) 20 IU/L, alanine transaminase (ALT) 28 IU/L, total protein 6.5 g/dL, serum albumin 3.4 g/dL, calcium 8.9 mg/dL, and phosphate 5.3 mg/dL. Proteinuria was 1 g per day. Antinuclear antibody and anti-DNA were negative. Computed brain tomography was normal (Figs. 1 and 2). Computed tomography (CT) of thorax and abdomen revealed a cavitary infiltration at right upper lobe and miliary reticulonodular opacity in both lungs, thickness of terminal ileum, and enlarged lymph nodes on mediastinum, mesenterium, retroperitoneum and axillae. Colonoscopy was performed. The histopathologic diagnosis of ileocecal lesions was chronic ulcerative inflammation. Presence of acid-fast bacilli was determined by aspiration of lymph node. The patient was treated with isoniazid (300 mg/day), rifampicin (600 mg/day), ethambutol (1 g/day), pyrazinamide (1.5 g/day) and pyridoxine (20 mg/day). He responded to anti-tuberculosis treatment and his vision returned to normal. In addition, his renal function improved and lymph nodes disappeared. At the last visit, 12 months later, his serum creatinine and BUN levels were 2.2 mg/dL and 34 mg/dL, respectively. Erythrocyte sedimentation rate had declined to 35 mm/hour.

Discussion

Sudden blindness may occur in patients with tuberculosis and tuberculosis meningitis. The most frequent causes of visual loss secondary to tuberculosis infection are neuroretinitis, intraocular tuberculosis, perichiasmal tuberculoma and optic disc tuberculoma (2–5). Neuroretinitis, intraocular tuberculosis and chiasmal tuberculoma have been reported as first manifestations of tuberculosis (2, 4, 5). Besides direct ocular manifestation of tuberculosis, significant reversible and irreversible loss of vision can occur during ethambutol therapy (6). The risk of toxic optic neuropathy is related to dosage and duration of therapy. The safe daily dosage of this agent is 15 mg/kg. Reaction commonly occurs at higher doses (25 mg/kg) and several months after initiation of treatment (7). But during the early period, lower doses of ethambutol can cause toxic optic neuropathy. Isoniazid can also cause toxic optic neuritis, but less frequently. Common risk factors of optic neuritis are diabetes mellitus, chronic renal failure, alcoholism and advanced age (8).

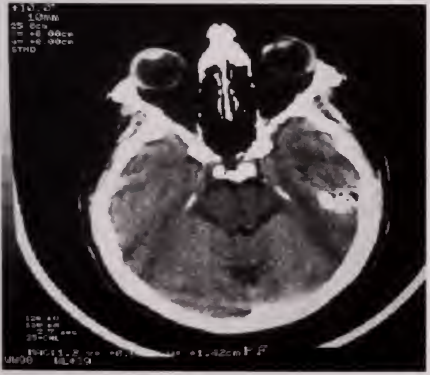

Fig. 1. Normal appearance of optic chiasma in computed brain tomography.

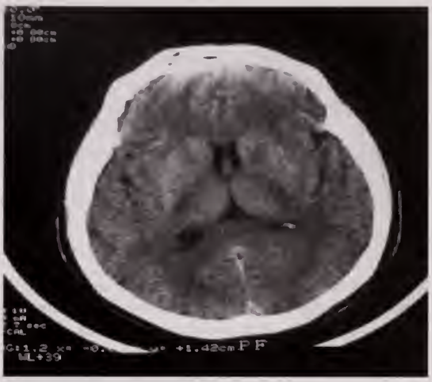

Fig. 2. Normal appearance of occipital lobe in computed brain tomography.

Our patient received multiple anti-tuberculous agents; the daily dose of ethambutol was 15 mg/kg. After 2 days of treatment visual loss occurred. After using intravenous corticosteroid prednisolone (100 mg), his vision improved. We suggest that his sudden blindness might have been related to tuberculoma, even though brain tomography was normal, because this test is less sensitive than magnetic resonance imaging (MRI). Anti-tuberculous treatment with a steroid is one proposed treatment for tuberculoma. The need for surgical treatment is rare (3). We did not perform orbital CT because his clinical manifestation and blindness diminished with anti-tuberculous treatment. Hepatic and optic complications were not seen attributed to the therapy. He showed improvement of renal function, with a stable creatinine clearance of 35 – 40 mL/min. Although ethambutol-related reversible blindness has been reported soon after treatment, loss of vision at the beginning of tuberculosis treatment may also be associated with the disease itself. Anti-tuberculous treatment with the supportive effect of steroid can prevent tuberculoma and neuroretinitis-related vision loss.

Conclusion

This case involved sudden blindness in a patient with disseminated tuberculosis. During the clinical course of disseminated tuberculosis, sudden loss of vision can be related not only to drug toxicity, but also to the disease itself (tuberculoma, etc.), and differential diagnosis is very important. Antituberculous treatment should not be interrupted until the main cause of vision loss is determined.

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Midterm Results of a Single-Center Experience with Commercially Available Devices for Endovascular Aneurysm Repair

Matthias Biebl, M.D.[1], Albert G. Hakaim, M.D.[1], W. Andrew Oldenburg, M.D.[1], Louis L. Lau, M.D.[1],
Joseph Klocker, M.D.[1], Beate Neuhauser, M.D.[1], Ricardo Paz-Fumagalli, M.D.[2], and
J. Mark McKinney, M.D.[2]

Abstract

Purpose: To review the outcome of endovascular abdominal aortic aneurysm repair (EVAR) using commercial stent graft devices.
Methods: Retrospective review of 167 EVAR procedures using different commercial devices at a single center between 1999 and 2003. Analysis included preoperative patient morbidities, operative and hospitalization data, postoperative complications, procedural outcome and midterm patient survival. Data are expressed as mean ± SD and total number (%). P-values ≤ 0.05 were considered significant.
Results: A total of 153 men and 14 women (mean age 75.0 ± 7.3 years, range 53.1–89.2 years) underwent EVAR. Technical success rate was 97.0%. Postoperative intensive care unit stay was 0.05 ± 0.24 days and hospital stay was 4 ± 1.84 days. Postoperative complications occurred in 25 patients (15.0%). Two patients had to be readmitted within 30 days. Median follow-up time was 16.0 months (0–48 months). Overall mortality rate was 9.6% and did not depend on the type of endograft used (p=0.287). No early or aneurysm-related deaths or aneurysm ruptures occurred. Clinical success rate was 91.6% (153 patients). Graft limb thrombosis occurred in 5 patients (3.0%), all with the AneuRx device (p=0.041). Graft migration was seen in 3 devices (1.8%). There were 36 endoleaks (20.4%), specifically 30 branch vessel (type II) and 6 junctional (type I) endoleaks. Early endoleaks occurred in 21 patients (12.5%) and late endoleaks in 15 (9.0%). Twenty-two patients (13.0%) required secondary procedures (75.0% catheter-based vs. 25.0% surgical). Three patients (1.8%) underwent conversion to open aortic repair, 2 (1.0%) within the first year after EVAR. Aneurysm sac stabilization or shrinkage (≥ 5 mm reduction in transverse aneurysm diameter) occurred in 98.2% of patients; aneurysm shrinkage rate was 39.6% at 1 year, 68.74% at 2 years and 79.96% at 3 years after the procedure. Time to aneurysm shrinkage was longest with the AneuRx (1.96 ± 0.18 years) and Talent (1.67 ± 0.53 years) devices, compared to the Zenith (1.01 ± 0.13 years), Ancure (0.95 ± 0.14 years) and Excluder (0.25 ± 0.17 years) stent grafts (p= 0.0001).
Conclusion: Endovascular aortic aneurysm repair using commercially manufactured devices is safe and effective, especially in patients at high risk for open aneurysm resection. While evolving endovascular experience has significantly decreased complication and secondary intervention rates, close long-term follow-up remains mandatory to detect late complications. Elective and unbiased use of all available surgical and interventional procedures is required to maintain long-term clinical success after EVAR.
Key Words: Abdominal aortic aneurysm, EVAR, commercial endograft, endograft migration, complication rate, secondary procedures, improved outcome, stent grafts.

List of Abbreviations

AAA: abdominal aortic aneurysm
ASA: American Society of Anesthesiologists
CI: confidence interval
CT: computed tomography
EF: ejection fraction
EVAR: endovascular abdominal aortic aneurysm repair
FDA: Food and Drug Administration
FEV1: forced expiratory volume at 1 second
ICU: intensive care unit
IDE: investigational device exemption
MI: myocardial infarction
PVB: paravertebral blockage
SD: standard deviation
VC: vital capacity

From the [1]Section of Vascular Surgery and [2]Department of Radiology, Mayo Clinic, Jacksonville, FL.

Address all correspondence to Albert G Hakaim, M.D., Section of Vascular Surgery, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224; e-mail: Albert.Hakaim@Mayo.edu

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Introduction

ENDOVASCULAR ABDOMINAL aortic aneurysm repair (EVAR) was introduced thirteen years ago (1) to prevent rupture of abdominal aortic aneurysm (AAA) in patients at very high risk for open surgical repair. Compared to open surgery, it requires shorter operative, intensive care and total hospital time; has lower postoperative morbidity; and allows for an earlier postoperative return to function (2–5). Such favorable results have made EVAR an attractive method for elective AAA repair (6–10), especially for octogenarian patients (11). With increasing device versatility, EVAR is currently the preferred treatment option for the majority of AAA patients (12).

However, growing experience has revealed that the durability of initial aneurysm exclusion is challenged over time by the pulsatile aortic blood flow and post-EVAR changes in aortic morphology. Related late adverse events after EVAR include endograft migration and kinking, separation of modular devices, and stent and graft fabric fatigue (13–18). Therefore, EVAR currently mandates long-term or even life-long follow-up (14–16) to avoid late aneurysm rupture (13). These problems are mirrored in high secondary procedure rates (19.6–29%) over midterm follow-up as reported in early endograft experiences (19–21). However, many of the device designs used in these early series failed to achieve recognition by the Food and Drug Administration (FDA). The endovascular armory, as well as the understanding of aortic remodeling, have been steadily refined since then. We report on recent developments and outcomes in EVAR, and our EVAR experience with commercial FDA-approved and investigational devices placed in patients between 1999 and 2003.

Patients and Methods

We did a retrospective review of all consecutive patients undergoing endovascular repair of infrarenal aortic or aorto-iliac artery aneurysms at our institution between June 1999 and December 2003. This study was approved by our Institutional Review Board; informed written consent was obtained from all patients prior to EVAR. The studied group comprised patients with commercial endograft designs (Table 1). Patients with custom-made devices and patients with previous endovascular treatment at outside institutions were excluded. Primary study endpoints included aneurysm-related survival, freedom from rupture, and freedom from secondary procedures (including conversion). Secondary study endpoints were overall survival, freedom from endograft migration, any type of endoleak, aneurysm enlargement, and postoperative complications. Data were abstracted from our prospective electronic endovascular database, and occasionally, additional information was obtained from paper medical records.

Patient Selection

Endovascular repair was offered to patients considered to be at high risk for open aortic surgery. This was defined as presence of significant cardiac comorbidities (e.g., stable angina, reversible or fixed perfusion deficit on stressed cardiac scan, myocardial infarction [MI] < 6 months prior to surgery, ejection fraction [EF] < 35%) or pulmonary comorbidities (e.g., vital capacity [VC] < 1.85 L, forced expiratory volume at 1 sec [FEV1] < 1.2 L, or < 35% of predicted, pulmonary hypertension, home oxygen use), known intolerance to general anesthesia, or hostile abdomen. A patient's preference was another reason for offering endovascular treatment.

TABLE 1

Commercial Stent-Graft Devices Placed

	Total	Male	Female	1999[*]	2000	2001	2002	2003
AneuRx *(Medtronic, AVE, Minneapolis, MN)*	90	85	5	8	28	23	15	16
Zenith *(Cook, Inc., Bloomington, IN)*	45	38	7	0	18	14	6	7
Ancure[†] *(Guidant, Inc, St. Paul, MN)*	12	12	0	0	2	5	3	2
Talent *(Medtronic, AVE, Santa Rosa, CA)*	18	16	2	0	1	0	3	14
Excluder *(W.L. Gore, Inc., Flagstaff, AZ)*	2	2	0	0	0	0	0	2
Total	*167*	*153*	*14*	*8*	*49*	*42*	*27*	*41*

[*] *Only November–December 1999 included.*

[†] *device withdrawn from market in June 2003 by company.*

Anatomical Suitability

Aneurysm configuration, proximal neck length and angulation, and iliac measurements were obtained by computed tomography (CT) angiography with 3 mm cuts, followed by 3-dimensional reconstruction. Circumferentially calcified small iliac arteries (< 7 mm diameter), a proximal neck with circumferential mural thrombus, extensive angulation (> 60 degrees to the main aortic axis), or an inverted funnel shape (> 10% increase in diameter over 15 mm length) were considered anatomic exclusion criteria. A proximal mid-neck diameter of less than 32 mm was acceptable for the Talent device, 28 mm or less for the Zenith, and less than 25 mm for the remaining devices. These differences originate from the different levels of proximal endograft anchorage: While the Zenith and Talent devices utilize transrenal fixation with bare proximal stents, the Ancure, AneuRx and Excluder devices anchor below the level of the renal arteries. Follow-up included physical examination, biplanar abdominal plain radiography and helical CT angiography at 1, 6 and 12 months post-procedure, and every 6–12 months thereafter. Once the maximum aneurysm sac diameter had decreased to approximately that of the stent-graft, the CT was substituted for ultrasound surveillance.

Definition of Success

Technical success was defined as successful vascular access, device deployment with no type I or III endoleak, and graft patency through the first 24-hour postoperative period. Clinical success was defined as absence of the following: AAA related death, any type I or III endoleak, AAA diameter enlargement > 5 mm, > 20% graft dilation, graft migration, device failure, aneurysm rupture, or early or late conversion to open repair. Due to inter-study and inter-observer differences, aneurysm shrinkage was defined as a decrease of 5 mm or more compared to preoperative values and sac enlargement as increase in transverse aneurysm diameter of 5 mm or more between any two studies.

Death was classified as operative death (within 30 days of surgery) or late death, either aneurysm related (secondary to aneurysm rupture or any primary or secondary procedure) or unrelated. Endograft migration was defined as caudal graft dislocation of more than 10 mm.

Endoleak Classification

Endoleaks were categorized as periprosthetic (type I: inadequate sealing of the attachment zone), branch vessel (type II: retrograde flow via an aortic side branch), or transgraft (type III: direct graft fabric defect or disconnection of modular graft components) endoleaks, or a blush of contrast inside the aneurysm sac through graft fabric porosity (type IV) (22, 23). Aneurysm enlargement in the absence of demonstrable perfusion was defined as endotension (type V). For time-to-endoleak analysis, all patients with detectable endoleak during follow-up were counted as positive for endoleak, regardless of whether the endoleak subsided, was treated, or persisted at the time of the last available follow-up CT study. Immediate treatment was recommended for all type I and III endoleaks. Uncomplicated type II endoleaks were observed, but treated in the presence of transverse aneurysm diameter increase of 5 mm or more if the patient experienced pain, or based upon the diameter of the AAA.

Statistical Analysis

Data are expressed in total numbers and percentages or mean values ± standard deviation (SD) and range. Dichotomous variables were compared with Chi-2 analysis and Fisher's exact tests. Numeric data were tested for normal distribution using the one-sample Kolmogorov-Smirnov test and parametric or non-parametric tests applied as indicated. Cumulative survival, time-to-endoleak and time-to-secondary-procedure were estimated using log-rank tests and the Kaplan Meier estimator. Statistical analyses were conducted with SPSS software (Version 10.0; SPSS Inc., Chicago, IL), and for all tests statistical significance was assumed if $p \leq 0.05$.

Results

Between November 1999 and December 2003, commercial endografts (Table 1) were used by 167 patients (91.6% male and 8.4% female). Mean transverse diameter of the treated aneurysms was 56.32 ± 8.78 mm (range 32–84 mm, one patient with a small AAA [< 50 mm] also had bilateral common iliac artery aneurysms). Patient comorbidities are outlined in Table 2. Patient assignment to a specific device was based upon anatomic suitability and, if the device was still investigational at time of treatment, our ability to treat high-risk patients based upon inclusion in an FDA-approved clinical trial (Talent).

General anesthesia was used in 89.8% of cases, while paravertebral blockage (PVB) (24) with conscious sedation was used in 7.2%, spinal anesthesia in 2.4%, and local anesthesia in 0.6%.

TABLE 2
Preoperative Patient Demographic and Medical Comorbidity Data

	Mean	SD
Age (years)	75.0	7.3
Weight (kg)	84.85	16.12
Height (cm)	174.15	8.46
	n	**% of Patients**
Age ≥ 80 years	43	25.7
Use of nicotine	76	45.5
Past	*55*	*32.9*
Current	*21*	*12.6*
Hypertension	115	68.5
Diabetes mellitus	21	12.6
Insulin dependent	*9*	*5.4*
Hyperlipidemia	93	55.7
Drug controlled	*78*	*46.7*
Carotid artery disease	42	25.1
History of TIA / stroke	*9*	*5.4*
Acute stroke / permanent deficit	*4*	*2.4*
Coronary artery disease	97	58.1
Unstable angina, MI < 6 months ago	*7*	*4.2*
Ejection fraction < 50%	61	31.8
Oral anticoagulation	17	10.2
Pulmonary	71	42.5
VC <1.85 l, FEV1 <1.2l, <35 % predicted, pO2 >45 mm Hg, home oxygen use	*8*	*4.8*
Renal	20	*12.0*
Creatinine >6.0, dialysis, post-transplant	*2*	*1.2*
Cancer	11	6.6
ASA score 2	14	8.4
3	131	78.4
4	21	12.6

TIA = transient ischemic attack, MI = myocardial infarction, VC = vital capacity, FEV1 = forced expiratory volume at 1 sec, ASA Score = American Association of Anesthesiologists Score.

Mean operation time was 180.4 ± 62.9 min. Intraoperative blood loss was 401.4 ± 392.0 mL. During the procedure, 21.6% of the patients received cell-saved autologous blood (89.0 ± 184.8 mL), while only 4.2% required packed red blood cell transfusion (0.2 ± 0.7 units). Total amount of intraoperative intravenous fluids was 3208.0 ± 1271.5 mL. Length of hospital stay was 4.0 ± 1.84 days (2–16 days), and while 95.8% of the patients required no postoperative intensive care, 3.6% of all patients were admitted to the intensive care unit (ICU) for 1 day and 0.6% for 2 days (overall mean 0.1 ± 0.2 days).

Initial endograft deployment was successful in all patients, and 24-hour technical success was 97.0%. Technical failure included partial coverage of a renal artery (1.2%), postoperative early graft limb thrombosis (0.6%), and postoperative type I endoleak (1.2%). At the end of follow-up, overall clinical success was 91.6%.

Primary Study Endpoints and Patient Survival

During the observed study period (mean 16.0 ± 13.0 months, range 0.1–48 months), there were no aneurysm-related deaths or aneurysm ruptures (0.0%).

The estimated cumulative overall survival for the observed time interval was 92.1% at 1 year, 84.7% at 2 years and 84.7% at 3 years. Postoperative survival was the same for all endograft groups (p= 0.287).

Secondary procedures after EVAR are listed in Table 3. Overall cumulative reintervention rate was 14.1% at 1 year, 15.6% at 2 years and 23.5% at 3 years (Fig. 1), with an estimated freedom from reinterventions at 1, 2, 3 years of 85.0%, 84.4%, 74.1% for the AneuRx, 83.1%, 83.1%, 83.1% for the Zenith, and 77.9%, 77.9%, 77.9% for the Ancure device groups, respectively (Kaplan Meier method, p= 0.883). One reintervention (7.1%) was required in the Talent and none (0.0%) in the Gore group. Conversion to open surgery (1.8%) was performed for aortic rupture during proximal aortic stent deployment (day 30), progressive suprarenal aneurysm formation (day 113) and en-

TABLE 3
Secondary Procedures (Interventional and Surgical) following EVAR

			Intervention	Surgery
Patients (%)	22 (13.2%)*		18 (72%)	7 (28.0%)
Type of Procedure	**n**	**%**		
Surgical conversion	3	10.7		x
Bypass (cross-over)	1	3.6		x
Graft limb thrombectomy	1	3.6		x
Inguinal wound revision	2	7.1		x
Angioplasty ± stent	5	17.9	x	
Additional proximal cuff	4	14.3	x	
Additional distal extension	2	7.1	x	
Embolization (coils/glue) of type II endoleak	10	35.7	x	
TOTAL	28+	100.0	21 (75%)	7 (25%)

* 3 patients underwent both interventional and surgical secondary procedures.
+ 1 patient underwent four unsuccessful attempts for embolization of a type II endoleak.

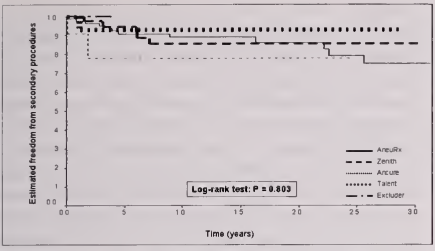

Fig. 1. Freedom from secondary procedures after deployment of commercial EVAR devices.

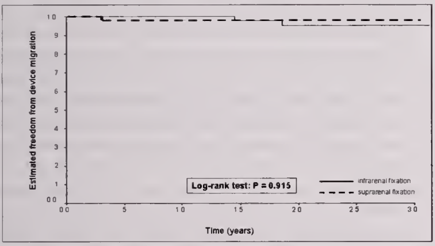

Fig. 2. Cumulative freedom from endograft migration for infrarenally (n = 104; drawn line) and suprarenally (n = 63; interrupted line) anchored devices (p=0.915).

dotension (day 935). Type II endoleak embolization was successful in 71.4% of attempted cases.

Secondary Study Endpoints

EVAR-related adverse events are shown in Table 4. Graft migration occurred in 1.2% of patients. With no differences with respect to endograft fixation, the overall cumulative migration rate at 1, 2 and 3 years was 0.0%, 5.1% and 5.1%, respectively (Fig. 2). Any type of endoleak at any time (16.7% type I, 83.3% type II) occurred in 21.6% of patients during follow-up. Cumulative probability of endoleak development was 15.5% at 1 year, 23.9% at 2 years and 32.2% at 3 years (Kaplan Meier method). The type of endograft used did not influence overall endoleak occurrence (p=0.804). Overall, 25.0% of the endoleaks resolved spontaneously, 30.6% were treated, and 47.2% were still present at the time of the latest available CT scan (all type II).

Aneurysm measurement during follow-up revealed maximum transverse aneurysm diameter decrease in 47% and aneurysm size stabilization in 51.2% of patients, accounting for a freedom from further aneurysm enlargement in 164 of 167 patients (98.2%) at the end of follow-up. Aneurysm enlargement was encountered in 1.2% of patients. Cumulative occurrence of shrinkage was 39.6% at one year, 68.7% at two years and 80.0% at three years follow-up. Time to occurrence of aneurysm shrinkage was longer in patients with AneuRx (1.96 years; standard deviation [SD] 0.18; 95% confidence interval [CI] 1.5997–2.3230) and Talent devices (1.67 years; SD 0.53; 95% CI 0.6438–2.7284), but shorter in Zenith (1.01 years; SD 0.13; 95% CI 0.7466–1.2635), Ancure (0.95 years; SD 0.14; 95% CI 0.6686–1.2281) and Excluder stent-grafts (0.25 years; SD 0.17; 95% CI 0.0–0.5876) (p=0.0001).

Early postoperative systemic complications occurred in 15.0% of patients. These included pneumonia (2.4%), respiratory insufficiency (0.6%), atrial fibrillation (1.8%), myocardial infarction (0.6%) and congestive heart failure (0.6%), as well as ileus (1.2%), bleeding duodenal ulcer (0.6%) and pancreatitis (0.6%). Multi-organ

TABLE 4

Aneurysm and Graft Related Adverse Events during Follow-up for Commercial Devices

	Total	AneuRx	Zenith	Talent	Ancure	Excluder
Patients (n)	167	90	45	18	12	2
Mortality rate (30 days) % (n)	0.0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Early endoleak rate % (n)	12.5 (21)	12 (11)	11 (5)	17 (3)	17 (2)	0 (0)
Late endoleak rate % (n)	9.0 (15)	13 (12)	7 (3)	0 (0)	0 (0)	0 (0)
Graft infection rate % (n)	0.0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Limb thrombosis rate % (n)	3.0 (5)	6 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Immediate conversion rate % (n)	0.0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1-year surgical conversion rate % (n)	1.0 (2)	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)

n = total number, conversion = conversion to open repair, early endoleak = endoleak detected on CT scan within 30 days after EVAR, late endoleak = de-novo endoleak arising later than 30 days after EVAR failure and sepsis each occurred in 0.6% of all patients. Decrease in renal function with an increase in serum creatinine > 30% compared to baseline occurred in 7.2% of patients. Two patients (1%) with pre-existing end-stage renal disease resumed dialysis after surgery. After 334 inguinal incisions, wound infection (defined as positive cultures and need for antibiotic treatment) rate was 1.5%, and incidence of lymphoceles 3.3%. Two lymphoceles required treatment, one by aspiration and one by surgical revision. Re-hospitalization rate within 30 days was 1.0% for bilateral groin infections and shortness of breath and occurrence of a proximal type I endoleak after implantation of an AneuRx device (1).

Twelve patients (7.2%) experienced problems related to their iliac limbs, including 5 total (all in AneuRx patients; p=0.041) and 1 partial occlusion, 2 stenoses, 1 graft kinking, 1 iliac artery laceration with intimal flap, 1 distal type I endoleak and 1 bad anchorage of the distal sealing zone. Two limb occlusions (40%) needed further interventions, while 3 nearly asymptomatic patients refused reintervention and were treated medically.

Discussion

First described by DuBost (25), open surgical repair of abdominal aortic aneurysms (AAA) provides excellent long-term results and has a low operative mortality in elective settings (1.4–4.0%) (26–28). Endovascular abdominal aortic aneurysm repair (EVAR) is a newer treatment strategy for AAA, with dramatically reduced operative pain, morbidity and length of hospital stay compared to open surgery. More important, EVAR allows for AAA repair in patients with severe medical co-morbidities who would otherwise be unsuitable for open treatment options.

In the setting of elective repair of an asymptomatic AAA, however, the favorable early results of EVAR have to measure up against the excellent mortality and long-term results of the open approach. While mortality after EVAR is low (1.5–2.6%) (29, 30) and similar to that of open repair, long-term durability has been an area of great concern for patients who participated in early series. To achieve stable fixation within the diseased vasculature, the endograft needs proximal and distal segments of unaltered aorto-iliac vessel in order to have correct position and tight sealing of the excluded aneurysm. Patient's aorto-iliac anatomy was unsuitable for early endograft designs in up to 90% (bifurcated grafts), while aorto-monoiliac grafts and transrenal fixation allowed for higher eligibility rates in 48–66%. The most common anatomic exclusion factor remains a proximal neck anatomy unsuitable for endograft anchorage. Narrow or tortuous iliac anatomy inadequate for device delivery is less frequent (12, 31, 32); however, early and more rigid device designs were often difficult to navigate through narrow or tortuous vessel segments, with increasing risk of access vessel laceration or even aneurysm rupture. EVAR series from 1994–1999 reported iliac access and femoral vessel complications in 9–13.9% (29, 33). Contemporary endografts are more flexible, with a long, tapered introducer tip to reduce shear forces during device advancement, and access-related morbidity declined substantially in a more recent series (34). In this series, only one iliac artery laceration (0.5%) occurred (Talent). Another vexing problem, especially with unsupported endograft designs (endograft fabric without internal or external supportive metal skeleton), was stenosis or thrombosis of the iliac limbs, resulting in reintervention rates as high as 38% (bifurcated Guidant graft) (35). These findings led to a more supported and rigid limb design, as used in modular stent-grafts. Surprisingly, all limb occlusions in our series occurred with the modular AneuRx endograft. Nevertheless, the resulting overall limb thrombosis rate of 3% (5% for AneuRx devices) is consistent with occlusion rates reported by other large series using the AneuRx graft, including a US multicenter trial (3% limb occlusion rate) (36). After successful graft deployment, postoperative remodeling of the excluded aneurysm can have major impact on the durability of the repair. Unlike open repair, continuing proximal aortic neck dilatation has been recognized as an important variable after EVAR (37, 38). During endograft deployment, the proximal device diameter is tailored to fit the aortic infrarenal diameter; ongoing dilatation compromises graft fixation and may lead to device migration and failure of aneurysm exclusion. Makaroun et al. reported progressive neck dilatation within 2 years in 20% of patients (39); endograft migration subsequently has been recognized to be time-dependent, similar to endoleak occurrence or postoperative survival after EVAR. Analysis of the AneuRx multicenter trial data found that low endograft deployment below the renal arteries and short proximal fixation zone length were more indicative of late migration than preoperative aneurysm morphology or proximal neck length (40).

Endoleak (reperfusion of the excluded aneurysm sac) formation after EVAR is also time dependent. The cumulative endoleak rate in this series of 23.9% at two years compares to other large series using multiple devices (29, 41), and unlike previous reports (42), we did not experience significant device-specific differences in endoleak rates. In the subgroup of endoleaks, however, the late (> 30 days after EVAR) endoleak occurrence was 3 times higher with the AneuRx device as compared to other devices. While this did not reach statistical significance, it was paralleled by slower aneurysm sac shrinkage in the AneuRx group. However, given the time-dependent manner of endoleak occurrence, we cannot exclude a type II error in our series, as the AneuRx device was the most commonly used, and those patients also had the longest postoperative follow-up. Device-specific differences in aneurysm involution rates have been reported previously, and in their large series from the Cleveland Clinic, Ouriel et al. also noted a trend towards an increased number of microleaks in AneuRx devices (41), which would support our results.

In earlier series, secondary procedures were reported in 29–38% of patients over midterm follow-up (35, 42). Improved device design and refined patient selection have significantly lowered secondary procedure rates. Contemporary results of second and third generation stent-grafts include lower re-intervention rates (15–20%) (16, 18). The midterm reintervention rate in this study compares favorably, with 11.9% of patients requiring an additional procedure.

Clearly, EVAR is a rapidly evolving technology, widely used by a variety of medical specialists (e.g., vascular surgeons, interventional radiologists, interventional cardiologists). However, of paramount importance is the commitment to ongoing follow-up by both physicians and patients, to ensure long-term aneurysm exclusion. EVAR is a new therapeutic option in the management of AAA, a potentially life-threatening condition, and rigorous long-term follow-up, if possible with prospective patient registries, has often been mandated (43). The recently reported nationwide EVAR experience from France from 1999–2003 (44), however, revealed how sobering real countrywide results for this new procedure can be. Thirty-day mortality (3.1%) and 1-year mortality (5.3%; 2.2% device and procedure-related) and complication rates (19.9%) were surprisingly high, with 31% of the aneurysms treated being smaller than 50 mm in diameter. In light of two large randomized studies (45, 46) demonstrating the low risk of spontaneous aneurysm rupture (< 1%) for such small aneurysms, these mortality rates seem even more unacceptable. Also, a complete lack of follow-up surveillance was reported for 18.6% of all patients. These data clearly indicate that EVAR can under no circumstances be considered a "single-session" treatment performed by interventionalists without commitment to or logistic abilities for ongoing patient care, regardless of specialty. With the optimum endograft design and mechanism of aortic fixation yet to be determined, responsible patient selection and reliable postoperative surveillance must ensure that the patient receives maximum benefit from this new technology.

Conclusion

EVAR is a frequently used, effective alternative to conventional open surgery, especially for selected patients with otherwise excessive operative risk. Rapidly evolving technology and growing experience continue to dramatically improve complication and secondary procedure rates, but favorable long-term outcome can only occur with meticulous follow-up, and early and elective secondary interventions. Unbiased and sophisticated use of all available endovascular procedures and devices, including staged use of endografts with different anchoring and landing zones, in combination with surgical procedures, is necessary to improve outcome and ensure durable aneurysm exclusion.

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Mesalamine-Induced Lung Injury in a Patient with Ulcerative Colitis and a Confounding Autoimmune Background:

A Case Report

Giovanni C. Actis, M.D.[1], Antonio Ottobrelli, M.D.[1], Sergio Baldi, M.D.[2], Ermanno Scappaticci, M.D.[2],
Vittorio Modena, M.D.[3], Enrico Fusaro, M.D.[3], Giulio Mengozzi, M.D.[4], and Mario Rizzetto, M.D.[1]

Abstract

Two years after being diagnosed with ulcerative colitis, a 57-year-old man taking oral mesalamine experienced severe respiratory distress due to left lung pleuropneumonitis. Eight months later, severe respiratory distress recurred due to right lung pneumonitis. Extraintestinal manifestations of inflammatory bowel disease or mesalamine-induced pulmonary injury were considered in the differential diagnosis, which was complicated by a history of aseptic meningitis and evidence of an ongoing autoimmune response. The implications of the case are discussed.

Key Words: Inflammatory bowel disease, lung injury, autoimmunity.

Case Report

A 57-YEAR-OLD MAN was diagnosed with left-sided ulcerative colitis (UC) in October 1994. The disease was controlled with oral mesalamine. Flare-ups were accompanied by symmetrical arthritis of the hands and knees, and required high-dose parenteral steroids. Maintenance azathioprine was begun in March 1996 but discontinued seven months later because of severe leukopenia. The patient's medical history was remarkable for aseptic acute meningitis in 1992; antinuclear antibodies (ANA) were first detected at that time. At presentation with UC, ANA were present in high titer (1:640) and found to react strongly with centromere protein B (CENP-B).

November 1996—First Admission

The patient complained of shortness of breath, cough, left-sided chest pain and fever (peak temperature, 39°C). His condition gradually worsened and after 2 weeks he was admitted to our intensive care unit (ICU) at the Ospedale Molinette. Physical examination revealed bronchial breath sounds and hepatomegaly. Pulmonary function tests indicated small airway obstruction

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From the [1]Department of Gastroenterology, Divisions of [2]Pneumology and [3]Rheumatology and [4]Clinical Chemistry Laboratory, Ospedale Molinette, Torino, Italy.

Address all correspondence to Giovanni C. Actis, M.D., Department of Gastroenterology, Ospedale Molinette, Corso Bramante 88, 10126 Torino, Italy; email: actis_g@libero.it

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and reduced CO_2 diffusion. Laboratory tests were unremarkable. Peripheral blood eosinophil count was normal. The P_aO_2 was 54 mm Hg, so oxygen was given. A computed tomographic (CT) scan showed condensed left lung parenchyma with basal atelectasis consistent with pleuropneumonitis (Fig. 1). The patient's condition was unaffected by wide-spectrum antibiotics, but he responded to a maximum standard dose of prednisone of 1 mg/kg/day. When the condition was stable, the hepatomegaly was investigated and a liver biopsy revealed cryptogenic cirrhosis without signs of biliary disease. The patient was negative for hepatitis A, B and C virus antigens. ANA were detected and the titer was 1:640. The patient denied alcohol abuse and was unaware of exposure to hepatotoxins. Upon steroid tapering, fever and pain rapidly returned and prednisone was again administered. The patient was discharged on a tapering prednisone dose of 35 mg/day. The mesalamine regime, initially prescribed at 800 mg twice a day, was increased to three times a day (Fig. 2).

July 1997—Second Admission

Seven months after discharge, the patient was admitted to our ICU for the second time because of right-sided chest pain, dry cough and fever. Blood tests revealed elevated erythrocyte sedimentation rate (ESR), C-reactive protein and fibrinogen. Immunological tests showed an ANA titer of 1:640, anti-double-stranded DNA antibodies and cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA). Total leukocyte and eosinophil counts were normal. Chest radiography showed right basal atelectasis and elevated diaphragm. Pulmonary embolism was ruled out by radionuclide scan. Culture of pulmonary lavage fluid was negative, so corticosteroids were given. Lung findings and hematological signs of inflammation cleared, and the patient was discharged. Prednisone was continued at 30 mg daily because of resting and exertional dyspnea.

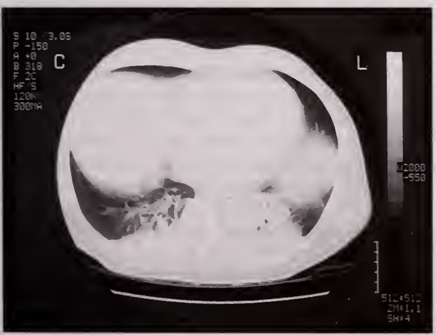

Fig. 1. Chest CT scan. Bilateral pleural reaction with an area of condensed parenchyma with air bronchogram suggesting pneumonia of the left lung.

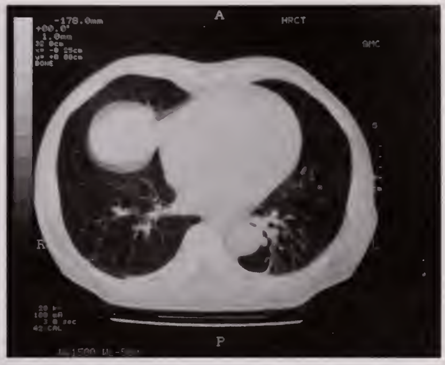

Fig. 2. Discharge chest CT scan. Significant clearance of the changes described above.

October 1997

Multiple vertebral fractures were diagnosed and steroids were tapered. Daily cyclosporine was started.

November 1997

One month later, mesalamine and steroids were suspended, but cyclosporine was continued.

January 1998

Six weeks later, only mild exertional dyspnea persisted. Otherwise, the patient felt well and showed no signs of active UC. Nailfold capillaroscopy revealed alterations of vessel walls, aneurysms and microhemorrhages compatible with connective tissue disease, and prednisone was given. Cyclosporine was continued. ANA titer was 1:320.

September 1999

Cyclosporine was discontinued after 22 months of treatment; prednisone (10 mg/day) was continued.

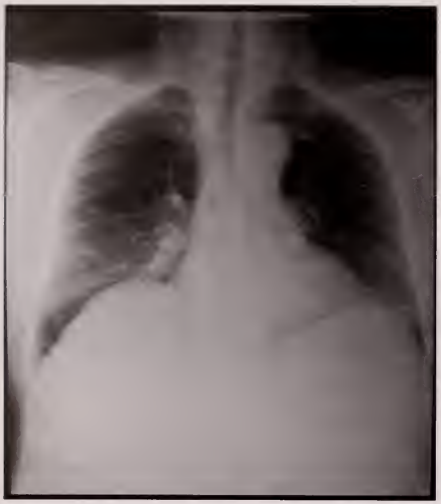

Fig. 3. Chest X-ray film. An elevated right hemidiaphragm (probably secondary to hepatomegaly) and bibasilar hypoventilation are the main changes in this outpatient repeat radiograph.

TABLE 1
Patient's Case History

Date	Condition	Medication
1994		
October	Active colitis	Local and oral mesalamine. Steroids.
1995		
July	Colitis relapse	High-dose oral steroids. Mesalamine.
1996		
March	Colitis relapse on steroid weaning	Azathioprine. Mesalamine. Prednisone 75 mg/day
July	Leukopenia	Azathioprine discontinued.
November	Left lung disease	High-dose parenteral steroids.
1997		
July	Right lung disease	High-dose parenteral steroids.
October	Dyspnea at rest Steroid toxicity	Mesalamine. Prednisone 35 mg/day.
November	Unchanged	Mesalamine discontinued. Prednisone tapering. Cyclosporine.
1998		
January	Exertional dyspnea	Prednisone tapering. Cyclosporine.
1999		
September	Improved	Prednisone 10 mg/day. Cyclosporine discontinued.
2000–2004		
September 2000 – September 2004	Good	Prednisone discontinued.

September 2004

At the time of writing, chest X-rays no longer show most of the previous changes (Fig. 3). The patient has been weaned from prednisone; he has not experienced further acute respiratory difficulty since July 1997. Aside from dyspnea upon strenuous exercise, he leads an active life.

Discussion

Up to 40% of patients with inflammatory bowel disease (IBD) present with extraintestinal manifestations of IBD that may involve bone, the biliary system, eyes and skin (1). In recent reviews, Storch et al. (2) and Foster et al. (3) illustrated the difficulty presented by the differential diagnosis of pulmonary abnormalities in IBD. In these reports, fifty cases of mesalamine- or sulfasalazine-related pulmonary abnormalities were documented; they consisted primarily of eosinophilic pneumonia characterized by the appearance of clinical symptoms within months of drug administration and the disappearance of symptoms upon drug discontinuation. These cases usually do not require intensive steroid treatment.

The case presented here (summarized in Tables 1 and 2) differs in many ways from other similar cases of IBD studied. First, pulmonary abnormalities appeared not months after, but two years after, mesalamine treatment began, a time lapse observed in only five other cases (2). Second, the patient improved after high-dose parenteral steroids, but his respiratory difficulties returned within hours of steroid withdrawal. Third, a positive c-ANCA test was found during maintenance treatment with mesalamine, an observation made in only three previous cases (2). For onset and course, our case is similar to the case of bronchiolitis obliterans described by Haralambou et al. (4). In our case, the pulmonary function tests suggested small airway obstruction, but lacked confirmation by lung biopsy. We conclude that this was an unusual

TABLE 2
Timecourse of Autoantibody Detection

Date	ANA[a]	Anti-ds DNA[b]	c-ANCA[c]
1996			
December	1:640	9	77
	1:640	9	75
1997			
March	1:640	ND	69
April	1:640	ND	<1.0
July	1:640	10	41
1998			
January	1:320	ND	<1.0
February	1:640	14	<1.0
March	1:640	10	<1.0
April	1:320	12	<1.0
June	1:640	ND	<1.0
July	1:640	ND	<1.0
September	1:640	ND	<1.0
August	1:640	13	<1.0
2000			
February	1:640	5	<1.0
March	1:640	5	<1.0
May	1:640	ND	<1.0

[a] Antinuclear antibody titer

[b] anti-double-stranded DNA antibodies; normal ranges 0–30 U/mL

[c] cytoplasmic pattern, antineutrophil cytoplasmic antibodies; normal ranges 0–20 U/mL

ND = not done

case of drug-induced pulmonary dysfunction in UC, the 51st such case recorded, according to our estimates.

It has often been emphasized that UC has an immunological basis, with the extraintestinal manifestations part of the common pathogenic mechanism (5). The presence of autoantibodies in our patient is evidence of immune system dysregulation. ANA were detected at a titer > 1:640 in all but two of the 14 tests performed between December 1996 and May 2000, with a centromeric pattern upon indirect immunofluorescence confirmed on 9 occasions. In addition, the capillaroscopic results are consistent with an autoimmune disorder. The episode defined as aseptic meningitis may be evidence of autoimmune-mediated end-organ damage; one convincing case of sterile meningitis as a harbinger of systemic lupus erythematosus (SLE) has been reported (6).

These findings raise the question of whether or not an underlying autoimmune disorder, possibly a lupus-like syndrome, is responsible for the array of inflammatory manifestations exhibited by this patient since 1992. Favoring this hypothesis are the following facts: (a) meningitis can herald SLE, (b) UC and SLE have been reported to coexist (7), (c) mesalamine can either cause or uncover SLE (8), and (d) the lungs are target organs in SLE (9). However, several points argue against a diagnosis of SLE for this patient, beginning with the fact that none of the classical criteria (10) are satisfied. Autoimmune lung disease in IBD often manifests itself as perinuclear-ANCA (p-ANCA)-positive vasculitis (2), but our patient was repeatedly p-ANCA-negative and he never showed signs of kidney dysfunction.

It remains difficult to determine the role played by cyclosporine treatment, prescribed at the time as a steroid-sparing agent. However, it seems reasonable to infer that mesalamine discontinuation alone prevented further disease recurrences. Since it remains unclear whether our patient is developing an ill-defined connective tissue disease (11) that facilitated or simply coincided with the recurrent pneumonitis, he is being kept under strict surveillance.

Conclusion

Inflammatory bowel disease should at times be viewed within the context of a more generalized immune imbalance affecting multiple organs, and not as an isolated pathological entity.

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Dean's Lecture

Recent Insights into Biological Regulation from Cell-Free Protein-Synthesizing Systems

Vishwanath R. Lingappa, M.D., Ph.D.[1], and Jaisri R. Lingappa, M.D., Ph.D.[2]

Abstract

We review the important role that cell-free protein-synthesizing systems (CFPSS) have played in the history of modern biology, and highlight two recent applications that illustrate their continued utility for the exploration of otherwise intractable aspects of gene expression and its regulation. Viral capsid assembly recreated in CFPSS reveals a catalyzed biochemical pathway involving transient, energy-dependent action of host proteins and discrete assembly intermediates, rather than the classical notion of self-assembly that was expected for capsid formation. Study of prion protein biogenesis reveals a new conformation critical for disease pathogenesis and advances the paradigm of *protein bioconformatics,* by which cells may productively regulate the folding of various proteins. In each example, the CFPSS made it easier to analyze biochemical mechanism than is possible in other currently available whole cell systems, illustrating why this approach is likely to be a continuing source of insight into important features of biological regulation.

Key Words: Protein synthesis, in vitro translation, biogenesis, protein folding, viral capsid, prion, wheat germ, reticulocyte lysate, translocation, endoplasmic reticulum, translocon.

Cell-Free Protein-Synthesizing Systems as a Tool for Studying Cellular Function

Protein synthesis is the primary biochemical process by which the information encoded in individual genes is expressed (1). Because of this central role in gene expression, the ability to carry out protein synthesis in a test tube, that is, to establish a cell-free protein-synthesizing system (CFPSS), can be a powerful first step towards understanding currently intractable features of biology. Many biological processes are difficult to study in humans. Investigating simpler model organisms, such as bacteria, yeast, worms, fruit flies, zebra fish, or mice (2–7) or using mammalian cells in culture (8), often makes new insights possible, provided that the features observed in those organisms, or in cultured mammalian cells, are shared with humans. The development and study of such model systems has accounted for much of the rapid progress achieved in our understanding of gene expression over the past two decades. It is important to recognize, however, that there are limitations to model organisms: bacteria don't have the intracellular organelles found in eukaryotes; yeast lack a dimension of complexity in intercellular communication observed in metazoans; and even mice are different from humans in important aspects of both normal physiology and disease pathogenesis (9). These and other confounding features limit the extent, albeit often substantial, to which the study of model organisms illuminates human biology and diseases (10, 11). Even human cells in culture, especially immortalized lines, can be highly aberrant compared to their tissue of origin (12). Thus, a complete understanding of biology comes from integrating results obtained using multiple approaches, each with different strengths and weaknesses.

Even when simpler organisms or cultured cells *do* provide insight relevant to human biology, another difficulty persists: many biochemical path-

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From the [1]Departments of Physiology and Medicine, University of California, San Francisco, San Francisco, CA; and [2]Department of Pathobiology, University of Washington, Seattle, WA.

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Address all correspondence to V.R. Lingappa, M.D., Ph.D., Department of Physiology, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143-0444; email: vrl@itsa.ucsf.edu

Glossary of Abbreviations

AR = autoradiography
ATP = adenosine triphosphate
C = carboxyterminal
CFPSS = cell-free protein-synthesizing system(s)
CHO = Chinese hamster ovary
CoA = coenzyme A
EM = electron microscopy
ER = endoplasmic reticulum
GSS = Gerstmann-Straussler-Sheinker
GTP = guanosine triphosphate
HBV = hepatitis B virus
HMWC = high molecular weight complex
Mb = membranes
MDR-1 = multidrug resistance gene-1
N = amino terminal
PK = proteinase K
PrP = prion protein
RMJ = ribosome-membrane junction
SARS = severe acute respiratory syndrome
SDS-PAGE = sodium dodecyl sulfate-polyacrylamide gel electrophoresis
Sec = secretory
SIV = simian immunodeficiency virus
SRP = signal recognition particle
StAR = steroidogenic acute regulatory
TrAF = translocation accessory factor
TRAM = translocation-associating membrane
TRAP = translocon-associated protein
WG = wheat germ embryo extract
wtPrP Tg = wild type PrP transgenic

ways are simply difficult to study in the larger context of other events happening at the same time within the cell. This is because living eukaryotic cells are: (a) *extremely complex*, with a bewildering array of interacting gene products and subcellular components (13); (b) *extremely crowded*, in terms of protein concentrations within the cell (14); (c) *incredibly fast*, in terms of the speed with which they are able to carry out biochemical events; and (d) surrounded by a *plasma membrane* that separates their inner workings from the outside world, obscuring the former from the prying eyes of the scientist. There are several general ways by which these difficulties have been dealt with, in order to gain insight into how events are integrated in the complex environment of living cells.

First, molecular genetics can be brought to bear in model organisms, through techniques such as gene knockout (15), transgene expression (16, 17), microarray analysis (18), and proteomics (19). One limitation of many of these approaches is that they do not inform us directly about protein-protein (or protein-nucleic acid) interactions that are the basis for biochemical mechanism (the knowledge of which is critical for pharmaceutical drug development, for example). Thus, a pathway may have steps and interacting partners that are not easily detected (20). Similarly, detection of a change in gene expression (e.g., by microarrays) doesn't provide insight into the mechanism involved. Molecular genetic analysis can also be confounded by the tendency of important pathways to have evolved redundant, alternate routes that allow an organism to survive, should a primary pathway be inactivated (21 – 23). Thus, it may only be under special circumstances (e.g., stress states) that deficiency of the primary pathway is fully manifested (24).

Second, biochemical approaches can be used to study molecular interactions directly — but at a price (Fig. 1; 25). Biochemical analysis is *reductionistic*: by isolating specific events away from the complex workings of the intact cell to varying degrees, biochemistry allows focus on a subset of events. Sometimes this is powerful, elucidating important but previously unappreciated molecular interactions. Sometimes it is misleading, because important interactions with other pathways within the cell are

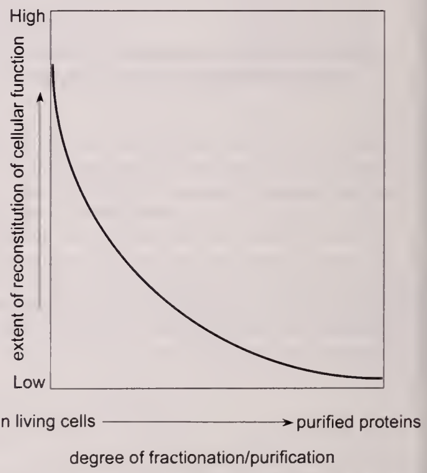

Fig. 1. Inverse relationship between the degree of purification of proteins and physiological relevance of the findings generated with those proteins. The greater the degree of protein purification, the more detailed is the resulting knowledge of the protein. However, the knowledge generated, while detailed, is missing key aspects of physiological relevance in rough proportion to the degree of purification and isolation of the proteins. This is a variation on the theme of the "Heisenberg Uncertainty Principle" as it applies to biology.

lost, and irrelevant ones can come into play. Often it is both, advancing our thinking in some ways, while misleading us on other aspects (26, 27).

At its extreme, the biochemical approach involves the study of purified proteins, in order to facilitate elucidation of their sequence and structure, and some aspects of function: for example, purified proteins are necessary to grow protein crystals whose X-ray diffraction patterns provide the most precise structural information. However, this approach cannot easily be applied to proteins whose function is intrinsically linked to other complex processes within the cell. Protein synthesis is an example of a linked process that is frequently ignored when proteins are studied in isolation. Synthesis of a protein and related post-translational modifications are often treated as separate from the function of the protein, but in doing so intrinsic relationships important within the cell may be missed. This limitation is quite significant, because protein synthesis and post-translational events are central to gene expression. However, as will be described below for specific examples, studies from CFPSS allow many events that are linked to protein synthesis and post-translational events to be reconstituted and thus make possible their experimental investigation with far greater fidelity than is often possible with purified proteins.

CFPSS can be used in two very different ways. In the more commonly used practice, it makes possible expression of the protein encoded by a gene of interest (28). This is typically performed using various commercial cell-free translation kits, and represents the *end* of the investigation (e.g., of the cloning and expression of a gene of interest). A second use of these systems is based on their ability to reconstitute other events that have a critical relationship to protein synthesis. Examples of steps that are different from protein synthesis, but have a special relationship to that process, include post-translational modifications, trafficking, assembly events, and various downstream protein-protein interactions, including some related to a protein's ultimate function. Thus, CFPSS can be used to study the biological mechanisms involved in the linked events, *while maintaining the connection to protein synthesis*. In this approach, the synthesis of the protein is *just the beginning*, providing the context in which other more functional aspects of gene expression/regulation can be explored. A critical issue is whether protein synthesis and subsequent linked post-translational and regulatory events observed in the CFPSS occur in a manner that faithfully reflects what occurs *in vivo*. In multiple examples, some of which will be discussed here, the fidelity of CFPSS has been corroborated by findings *in vivo*. The power of this use of CFPSS has not been fully appreciated by many biochemists and molecular biologists, and is the focus of the present review.

To prepare a CFPSS, plant or animal tissues are chosen that are specialized and/or primed for production of new proteins. For example, simple addition of water to seeds results in activation of dormant biochemical pathways in the embryo, including a burst of protein synthesis. This makes wheat germ embryo extracts (WG) a powerful starting material for preparation of a CFPSS (29, 30). Likewise, reticulocytes (immature red blood cells) are highly focused on production of a single protein, globin (the protein component of hemoglobin, which serves to carry oxygen in blood), making them an excellent starting material from which to prepare a CFPSS (rabbit reticulocyte lysate, RRL) (31, 32).

CFPSS start with a *crude extract* made from disrupted cells. Typically, initial disruption is carried out by homogenization, a process by which cells or tissue samples are subjected to shearing forces that mechanically break open cells. The resulting *homogenate* is then subject to centrifugation to remove unbroken cells and some large subcellular components that have been experimentally found to interfere with new protein synthesis. Disruption of the plasma membrane renders the cytoplasm and its organelles directly accessible to the experimenter. The resulting preparation contains all cytoplasmic proteins and many membrane-delimited organelles present in the cytoplasm, and is capable of synthesis of proteins *de novo*, when provided specific mRNA, amino acids, energy substrates and other components, and warmed to physiological temperatures. If one of the added amino acids is radiolabeled, it becomes possible to distinguish the newly synthesized protein encoded by the added mRNA, from the multitude of other proteins present in the crude extract, by analyzing the extract after completion of protein synthesis, by gel electrophoresis (Fig. 2). The ability to track the radiolabeled protein of interest as it interacts with unlabeled proteins of the cellular extract greatly simplifies analysis of various biochemical pathways that are in one way or another linked to protein synthesis. For example, the radiolabeled protein can be examined in the minutes following completion of synthesis to determine post-translational modifications or protein-protein interactions that may be necessary for a protein's function, measured separately in parallel aliquots. The extract itself can be subjected to varying degrees of manipulation prior to, during, and after protein synthesis, which can facilitate its use as an experimental system, as will be discussed below. Subcellular fractions can be removed or added before or

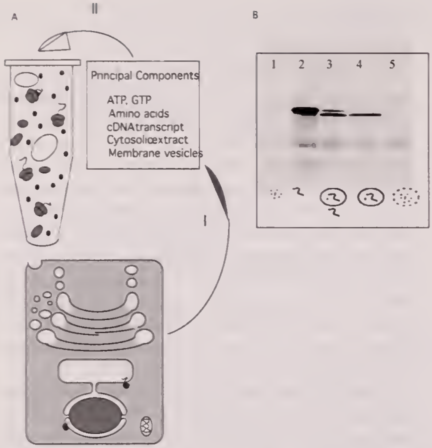

Fig. 2. Cell-free protein-synthesizing systems (CFPSS). (A) Schematic description of the components that comprise the CFPSS and their source. Cells are fractionated (I), and extracts prepared with or without various subcellular fractions, and (II) added to test tubes containing the energetic (e.g., adenosine triphosphate [ATP], guanosine triphosphate [GTP]) and substrate (e.g., amino acids, including one radiolabeled) requirements for protein synthesis and mRNA (e.g., cDNA transcript) encoding a particular protein of interest. When the mixture is warmed, specific protein synthesis proceeds in it, with the encoded (newly synthesized) protein radiolabeled. If microsomal membranes are present in the extract and the mRNA encodes a secretory or integral membrane protein, targeting to and translocation across the ER will occur. Newly synthesized proteins are distinguished from pre-existing proteins, because incorporation of the radiolabeled amino acid allows detection by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and autoradiography. **(B)** An autoradiograph of an SDS gel analyzing a reaction such as described in (A), where the translated polypeptide is a secretory protein (in this case, prolactin). Translation in the absence of added microsomal membranes is shown in lane 2. An aliquot of the material applied to lane 2 was first digested with proteinase K (PK) under standard (mild) conditions, resulting in complete degradation of the protein (see lane 1). Similar results are obtained when microsomal membranes are added after completion of protein synthesis, because only the *nascent* chain can target to the ER membrane. Lanes 3–5 show translation in the presence of added microsomal membranes. Lane 3 displays products after no other treatment. Note cleavage of the signal peptide, resulting in a small shift to lower molecular weight for most of the chains. Lane 4 displays the products after digestion with PK under mild conditions, with membranes intact. Note that the signal-cleaved form is protected from PK digestion because it is within the membrane vesicle, as a result of translocation. In Lane 5, the PK digestion takes place in the presence of nondenaturing detergent to abolish membrane integrity, rendering the protein fully accessible to PK. A schematic description of the consequences of each manipulation is shown at the bottom.

after carrying out the protein synthesis reaction, depending on the question of interest. For example, when microsomal membranes derived from the endoplasmic reticulum (ER) are added prior to start of synthesis, they will engage secretory or membrane protein signal sequences and initiate transport of those nascent chains into the ER, the first stage of the secretory pathway (33–35). Thus, *temporal relationships* can also be appreciated. To continue the previous example, adding microsomal membranes more than a few minutes after initiation of protein synthesis results in failure of translocation of a newly synthesized chain, reflecting a need for precise timing of protein-protein interactions necessary for translocation of newly synthesized proteins across the ER membrane (36).

A number of characteristics of the CFPSS make it particularly useful for dissection of the molecular mechanisms involved in biological regulation. These features enable one to overcome problems that made analysis in living cells difficult in the first place (Table). First, empirically, the events that do occur in the CFPSS have been found to be remarkably *faithful* to the corresponding events in living cells. Second, while mechanistically faithful, the CFPSS tends generally to be relatively *slow and inefficient*, compared to the same process occurring in living cells. This proves to be a most fortuitous characteristic, in that it allows events that take place too rapidly to be detected and studied easily *in vivo*, to be slowed down enough for analysis in the CFPSS. Much as a slow-motion replay of a videotape would reveal the sleight-of-hand by which a magician carries out his/her tricks, so analysis in a CFPSS can reveal features previously undetected in living cells. In some cases, armed with knowledge of the characteristics of a biological process from study in CFPSS, it has been possible later to reinvestigate the process in cells—and detect the signature features of the pathway that were originally missed, as will be discussed in greater detail for two examples below (37, 38).

Third, CFPSS tend to reconstitute only a subset of the events observed in cells. As a result, that subset of reconstituted events is magnified and enhanced by the CFPSS—put, as it were, under a molecular spotlight. In some cases, a blockade that prevents a pathway from proceeding beyond a certain

TABLE
Notable Features of CFPSS

Fidelity to events *in vivo*
Slow-motion compared to events in living cells
Focused on a subset of events observed *in vivo*
Amenable to manipulation in *cis*
Fractionation and reconstitution in *trans*

CFPSS = cell-free protein-synthesizing system(s) point can be used to further limit the progress of events in the CFPSS, for example, by adding or subtracting components, by changing reaction conditions, or through programming the CFPSS with mRNAs encoding mutant proteins. All of these manipulations make the study of molecular mechanism easier (39, 40). In this way, the *relationship* of early steps to later ones can be elucidated and explored.

Fourth, these systems are amenable to manipulations that cannot be done easily *in vivo*. For example, if the mRNA added to the CFPSS is prepared from a cDNA truncated upstream of the termination codon, the ribosome engaged in synthesizing the protein will be maintained at the point of truncation (due to the absence of a termination codon), thereby providing a prolonged *snapshot* of interactions occurring on the nascent chain at that point in chain growth (41, 42).

A fifth advantage of the CFPSS is its ability to be fractionated and subsequently reconstituted from relatively purified components, allowing proteins responsible for core biochemical activities to be distinguished from those involved in biological *regulation* (43–45).

A Brief Intellectual History of CFPSS

Modern biology is the epitome of an inductive science: almost nothing in it can be safely concluded from deductive first principles. Hypotheses that may seem implausibly complex at one point in time are often supported by experimental studies later (46, 47). Thus, new experimental data frequently “trump” older theories that are based on more limited working hypotheses. Conversely, no matter how well we *think* we understand a biological process, we can never exclude the possibility that there are as-yet-unappreciated steps that intervene between any two currently known steps. Rather, we can anticipate that future experimental findings will enrich, revise, and even overturn our thinking about things that we feel quite confident of today.

Classical biochemistry was born in the 1800s with the recognition that enzymes could be studied outside of cells (48), thus overturning the earlier physiological notion that the distinctive features of life could not be studied outside of living organisms (49). The power of this approach was demonstrated by the rapid progress made in analyzing biochemical pathways over the past century (50).

Similarly, cell biology, or *biochemical and biophysical cytology*, as it was once known (51), was born with the development of methods to look within cells. Previously, “protoplasm,” the stuff of living cells, was not seen as something that could be rationally and systematically separated into distinctive components. However, the observation of obvious membrane-delimited compartments in cells, using the electron microscope (52), motivated the development of techniques for separating subcellular components by fractionation using ultracentrifugation of homogenates (53, 54).

Once organelles were defined by electron microscopy and correlated to specific enriched fractions generated by ultracentrifugation of cellular extracts/homogenates, the stage was set to use pulse-chase radiolabeling of cells, followed by subcellular fractionation and electron microscopic autoradiography, to define trafficking of proteins from their site of synthesis through their lifecycle (55–58). In this way, the *secretory pathway* by which proteins are transported out of the cell (secreted) was defined as a cell biological process (59; Fig. 3a).

The earliest step in protein secretion, namely translocation of the nascent chain across the membrane of the ER, proved to be a particularly delicate experimental challenge, because it occurs *while* the protein of interest is being made (Fig. 3b). This is a situation in which the focus of interest (i.e., the nascent chain), is constantly changing with the addition of amino acid residues, and thus, is not at equilibrium. For this reason, ferreting out the secrets of ER translocation involved some remarkable manipulations. First, systems were established in which protein chains that had been initiated *in vivo* were completed in cell-free extracts (60, 61). This set the stage for development of systems in which protein synthesis occurs *de novo*, i.e., the CFPSS. In those systems, the first step in the secretory pathway (translocation across the ER membrane), was reconstituted only if a particular subcellular fraction derived from the ER (termed “microsomal membranes”) was added (34, 62). Experiments in this system made it possible to appreciate a fundamental function of the ER: to initiate the sorting of *nascent* proteins destined for secretion from those destined to remain in the cytoplasm. These studies also elucidated the role of signal sequences in directing the nascent chain to receptor proteins that target the ER membrane, and explained why the ER membrane is typically studded with ribosomes engaged in the synthesis of (signal-sequence bearing) nascent chains. Finally, it was demonstrated that signal sequences were being removed *while the chain was still being made*, explaining why pulse-chase analysis of living cells generally failed to demonstrate a precursor-product relationship between completed, signal-sequence-containing, newly synthesized proteins and the mature, signal-sequence cleaved form

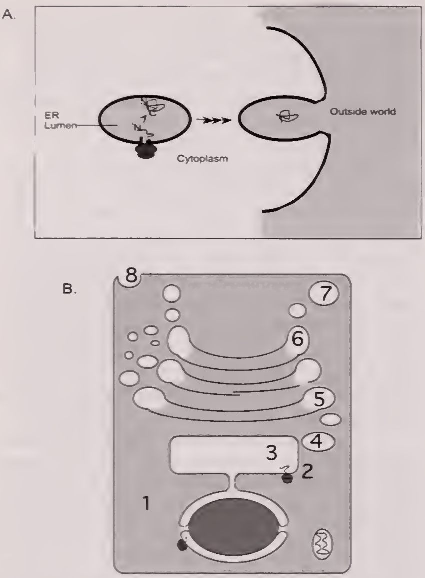

Fig. 3. Early events in protein biogenesis at the endoplasmic reticulum (ER). (A) Schematic representation of the ribosome-membrane junction (RMJ) at the ER and its relationship to the cell surface. Shown is the classical "closed" RMJ. Recent insights into protein bioconformatics demonstrate a newly appreciated level of complexity in this step of translocation. In the simplified example shown, the cytoplasm is white and the ER lumen is gray on the left. Ultimately, fusion of a vesicle derived from the ER with the plasma membrane exports products out of the cell. Note that the ER lumen is topologically contiguous with the outside world (also depicted as gray). **(B)** Outline of the major steps in the secretory pathway encompassed by the arrows between the vesicle and cell surface in A. Numbers refer to the major compartments traversed by a typical nascent secretory chain: (1) cytoplasm; (2) cytoplasmic face of the ER membrane; (3) ER lumen; (4) post-ER intermediate compartment; (5) cis-Golgi cysternae; (6) trans-Golgi cysternae; (7) secretory vesicles; and (8) exocytosis into the outside world.

(33). The importance of this lesson is often underappreciated: some biological processes are extremely difficult to "see" in living cells; the CFPSS offers opportunities to manipulate biochemical processes in ways that allow complex temporal and other special relationships between proteins to be analyzed and understood.

Much progress in understanding the function of the ER have been achieved since establishment of the new paradigm of protein targeting to and translocation across the ER membrane, as epitomized by the signal hypothesis (33). Most of these new insights were generated first from studies using CFPSS (34). For example, the role of specific protein complexes, namely signal recognition particles (SRP) and SRP receptors was deciphered through modern variations on classical biochemistry: protein purification, manipulation and reconstitution (63–66). Some key insights into the mechanism of translocation from studies in the CFPSS included: (a) the role of SRP in translational pausing (67); (b) the role of guanosine triphosphate (GTP) as a regulatory mechanism for SRP/SRP receptor dynamics (68, 69); (c) the role of a special *protein-conducting channel* now termed the *translocon* (47); (d) the special role of SRP-receptor biogenesis in bypassing the general restrictions to protein traffic at the ER (70); and (e) the role of the ribosome-membrane junction (RMJ) as a novel point of regulation of chain translocation to the ER lumen (71). Most recently, studies of specialized nascent chains have revealed that the signal sequence plays an unexpected and still poorly understood role in distinguishing various pathways by which the chain can traverse the ER membrane (72).

While the focus of this discussion is the CFPSS, we do not mean to underplay the importance of other approaches to these difficult problems. For example, the Sec 61 complex of proteins that comprises the ER translocon was first identified as essential for secretion by a genetic approach in yeast (73). Likewise, the notion that not all secretory and membrane proteins are SRP-dependent also emerged from the study of yeast genetics (21). The point is that genetic and biochemical approaches complement one another. In particular, the CFPSS is often crucial for dissecting and understanding the details of protein-protein interactions (74, 75). The ER is not the only subcellular location whose function has been elucidated in significant measure by studies in CFPSS. Important post-translational protein-protein interactions in the cytoplasm (39, 40) (see below), the Golgi apparatus (76), and the mitochondria (77) have also been elucidated by studies of related cell-free systems.

Viral Capsid Assembly

In the last decade, CFPSS have provided provocative data for a new view of the mechanism of assembly of viral capsids. This process, by which a large, ordered, multimeric structure (the capsid) is assembled post-translationally from monomeric polypeptide units within the complex environment of the cytoplasm, has eluded biochemical dissection using other approaches, for many of the reasons discussed above. Here we will describe the rationale for using CFPSS for studying capsid assembly, the results obtained to date using such a system, and the implications of these findings for our understanding of virus cell biology.

While viral life cycles are extremely varied, some common themes emerge across many virus families (Fig. 4). The early events in the life of most viruses involve virion entry, virion disassembly, and replication of the viral genome, with different virus families using diverse strategies, cellular factors, and cellular compartments to achieve these goals (78). In contrast, the goal of the late events of the viral life cycle is production and release of new virions. Co-ordination to maximize virion production is critical for the success of the virus, and viruses have evolved diverse mechanisms for ensuring effective formation of infectious virions (Fig. 5).

The first step in virion formation involves assembly of the capsid, within which the viral genome and viral regulatory proteins are housed and protected. In the case of enveloped virions, the capsid subsequently acquires an envelope from host lipid bilayer membranes and undergoes release, directly or by a more circuitous process, into the extracellular space before, or in some cases after, maturation (79). For many viruses, the process of capsid formation within cells is less well understood than virion budding and release. Typically, viruses are described as having either spherical or helical capsids, based on electron microscopic images of capsid shape. Enveloped viruses from a number of unrelated families, including Togaviridae, Flaviviridae, Retroviridae, and Hepadnaviridae, form spherical capsids in the cytoplasm of eukaryotic host cells, often at the cytoplasmic face of a specific membrane compart-

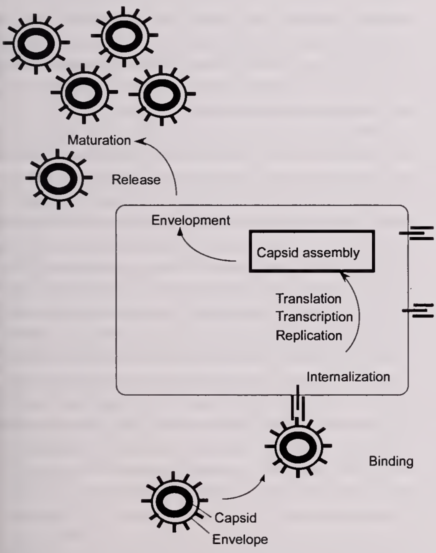
Maturation
Release
Envelopment
Capsid assembly
Translation
Transcription
Replication
Internalization
Binding
Capsid
Envelope

Fig. 4. The viral life cycle. Schematic representation of the typical steps in the life cycle of an enveloped virus. Note that each viral family represents a unique variation on these themes; nevertheless, they must all bind to their unique receptor, internalize, replicate, transcribe and translate their proteins, assemble their capsids, and be released. In some cases, maturation occurs as a separate step or concomitant with release. Of these steps, capsid assembly has been a "black box" long ascribed to self-assembly.

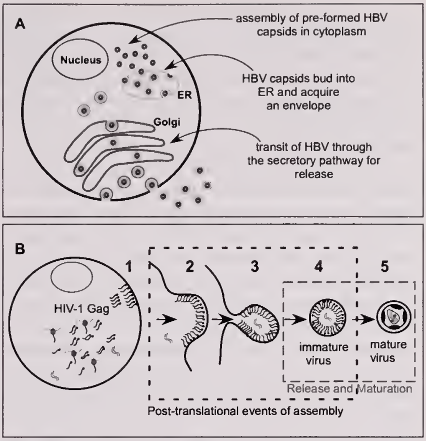
A
Nucleus
ER
Golgi
assembly of pre-formed HBV capsids in cytoplasm
HBV capsids bud into ER and acquire an envelope
transit of HBV through the secretory pathway for release
B
HIV-1 Gag
1
2
3
4
5
immature virus
mature virus
Release and Maturation
Post-translational events of assembly

Fig. 5. Overview of hepatitis B virus (HBV) and HIV assembly. (A) HBV capsids are composed of 180 or 240 copies of the HBV core protein that assemble into a 30 nm spherical capsid in the cytoplasm. These pre-formed capsids target to the endoplasmic reticulum (ER) membrane, where they are thought to exit the cell by traversing the secretory pathway. **(B)** The immature HIV-1 capsid is composed of close to 5,000 copies of the Gag polypeptide. Gag polypeptides are synthesized in the cytoplasm of the infected host cell and co-translationally myristoylated (1). Myristoylated Gag polypeptides target to the plasma membrane (2), which is where assembly of the spherical immature capsid occurs (3). As assembly of the 100 nm immature capsid is completed, it undergoes budding and envelopment by the plasma membrane, resulting in release of the immature virus particle (4). Subsequently, proteolytic cleavage of Gag mediated by the HIV-1 protease results in production of mature virus particles that have condensed, bullet-shaped capsids (5). Note that capsid formation of HBV and HIV involves coordination with encapsidation of the genome as well as packaging of viral and cellular proteins and factors that are critical for virus infectivity (not shown).

ment such as the plasma membrane or ER. Examples of viral families with helical capsids include the Filoviridae such as Ebola virus and the Coronaviridae, including the virus causing severe acute respiratory syndrome (SARS). To date, only assembly of viruses with spherical capsids has been studied in CFPSS.

Viruses have evolved the means to assemble their capsids efficiently in the very crowded environment of the eukaryotic cytoplasm. The process of capsid assembly within the cell in the context of a viral infection may be extremely complex. Depending on the virus type, hundreds or even thousands of copies of a capsid protein are organized to form a single viral capsid. For example, a single hepadnavirus capsid is typically composed of either 180 or 240 copies of the viral core polypeptide, and a retroviral capsid is composed of thousands of viral Gag polypeptides. In addition, the viral genome is typically selected from a large pool of RNAs within the cytoplasm and packaged with appropriate stoichiometry during capsid formation (80). Furthermore, some viral capsids contain a large number of other viral proteins that also must be selectively packaged within the newly formed capsid. For example, human immunodeficiency virus (HIV-1) contains 15 viral proteins in addition to two copies of genomic RNA (81). Finally, capsid formation must be synchronized with the subsequent steps of envelopment and occur at the correct subcellular location to result in proper virion release. Thus, assembly of spherical capsids in the cytoplasm of an infected eukaryotic cell is most likely carefully regulated and highly coordinated.

From the vantage point of modern cell biology, it is clear that one must take into account the cytoplasmic environment where capsid formation occurs, to fully understand the mechanism of viral capsid formation. The cytoplasm is likely to be a source of obstacles and antiviral pathways that the virus must overcome or counteract for successful capsid formation. However, it could also be a source of factors and organelles that viruses have learned to commandeer in order to facilitate the process of capsid assembly. In fact, it is likely that the evolution of viral capsid assembly mechanisms was profoundly shaped by both obstacles and facilitators present in the ancient cytoplasm.

The question of how capsids assemble can be addressed on many levels. First, there is the question of how individual capsid proteins interact with each other and with other capsid components. On a larger level, there is the question of how these individual capsid protein interactions are influenced by post-translational events, cellular proteins, the cytoplasmic environment, and organelles. Yet another level of complexity is introduced by studying sequential steps (discrete intermediates) in the formation of the capsid, and these need to be characterized in both time and space. Thus, capsid formation consists of sequentially occurring biochemical interactions with specific cellular proteins and organelles. The resulting complexes may be changing their subcellular location over time. Furthermore, these complicated events are probably subject to regulation, with molecular switches governing choices of pathways at each step in the temporal and spatial progression. Ironically, but not surprisingly, the question of how spherical capsids assemble was first addressed in an environment devoid of all cytoplasmic proteins or organelles during the 1970s. This was largely due to the growing awareness, during that time period, of the power of classical biochemical reductionism to provide a molecular view of a biologic process. Purified capsid proteins incubated in a buffer at extremely high concentrations (e.g., mg/mL) were found to have an intrinsic ability to "self-assemble" into spherical capsids. Such self-assembly was found to be typically promoted or "nucleated" non-specifically by oligonucleotides (Fig. 6a). This is perhaps best exemplified by seminal studies on tobacco mosaic virus (82), but has also been shown for retroviruses, flaviviruses, alphaviruses and other viruses, including phage and plant viruses.

While revealing an important property of capsid proteins, these self-assembly studies failed to take into account critical features of capsid assembly as it occurs in the context of the cell. These include the fact that, in cells, capsid assembly takes place in a cytoplasmic environment crowded with other proteins and processes, and occurs very, very quickly. A major contribution of CFPSS is their ability to allow assessment of such features, rendered difficult to assess by the conditions in living cells. In CFPSS, as in cells, the concentration of capsid protein is relatively low compared to the concentration of other (host) cytoplasmic proteins, which is as high as 300 mg/mL (83). This contrasts with the study of capsid proteins in isolation, in which the very high concentrations of capsid protein needed to drive the assembly reaction and cellular proteins are completely absent. A second critical feature common to cells and CFPSS is that capsid formation is temporally linked to translation of capsid proteins. In contrast, self-assembly systems use purified proteins, typically produced recombinantly from *Escherichia coli* and either purified in native form or denatured and renatured. Finally, cellular organelles, including membrane-bound compartments, are completely absent in recombinant self-assembly systems.

Nevertheless, despite these limitations, until the 1990s capsid assembly was studied largely using such self-assembly systems, combined with crystallography and mutational analysis of viral capsid proteins expressed in cells. Little was done to investigate the notions that cellular proteins could be involved in capsid formation, and that the pathway utilized by viruses in living cells might be different from that observed for self-assembly reactions. A notable exception to this trend was the demonstration that assembly of phage lambda heads fails to occur in the presence of mutations in the host bacterial GroE gene (84). Subsequent studies revealed that GroEL is a molecular chaperone involved in proper folding of newly synthesized proteins including phage lambda capsid proteins (85). In addition to ushering in the novel concept of molecular chaperones, these landmark studies introduced the idea that cellular factors may play a critical role in the viral life cycle by facilitating proper folding and assembly of viral structural proteins.

The first use of CFPSS for virion formation occurred in the early 1990s. In this system, infectious poliovirus was produced by programming a HeLa cell extract with poliovirus mRNA, demonstrating that CFPSS can faithfully reproduce all aspects of virion formation (86, 87). Subsequently, CFPSS was used to explore the mechanism of capsid assembly using hepatitis B virus (HBV) as a model system (40). The HBV capsid is relatively simple compared to other spherical capsids, and can be formed in both prokaryotic and eukaryotic cells simply by expression of the capsid protein. During infection, HBV capsids associate with the HBV envelope protein in the host ER, bud into the ER, and then traverse the secretory pathway for release outside the cell (88). Newly synthesized HBV capsids made in a CFPSS containing a wheat germ extract, closely resemble authentic HBV capsids by biochemical criteria (velocity sedimentation, buoyant density and protease resistance) and by the gold standard of electron microscopy (EM), demonstrating the fidelity of the system (40). Characterization of the steps involved in HBV capsid assembly in the CFPSS allowed the mechanism of HBV capsid assembly in *a cellular context* to be examined biochemically for the first time. Pulse-chase experiments in the CFPSS revealed that the HBV core progressed post-translationally through a high molecular weight complex (HMWC) with the characteristics of an *assembly intermediate*, before forming completed capsids (39). Characterization of the HMWC using immunoprecipitation revealed that it contained a cellular factor antigenically related to the molecular chaperone TCP-1. Furthermore, when the HMWC-containing HBV core and the cellular factor were isolated from CFPSS, capsids could be generated by manipulation of this complex using energy substrates and other treatments (40). These findings suggest an alternate mechanism for capsid formation involving a *facilitated*, energy-dependent pathway, which proceeds via a discrete intermediate with cellular factors playing transient catalytic roles. This is very different from the previous notions of capsid formation through self-assembly.

The view of capsid assembly as facilitated, step-wise, and energy dependent was elucidated in more detail in a second and more challenging case. A CFPSS was established in which assembly of the immature capsid of HIV-1, a retrovirus, was achieved (39). Both the structure and the assembly pathway of the HIV-1 capsid are significantly more complex than that of HBV (89). The Gag polypeptide, the primary constituent of the HIV-1 capsid, undergoes a co-translational modification in which a 14-carbon fatty acid, myristic, is added to its N-terminus. Myristoylation in combination with specific N-terminal Gag domains targets Gag to the cytoplasmic face of the host cell plasma membrane, which is where the events of capsid assembly occur. Once the completed HIV-1 capsid is formed, it becomes enveloped by the plasma membrane, resulting in direct release to the extracellular space without traversing the secretory pathway (Fig. 6). Membrane targeting is thought to play an important role in concentrating Gag chains to a threshold required for assembly (90), although this remains to be demonstrated experimentally.

Thus, the challenge of establishing a CFPSS for HIV-1 capsid assembly was to reproduce the requirement for co-translational myristoylation and targeting to the cytoplasmic face of membranes. By adding purified myristoyl coenzyme A (CoA) and subfractionating wheat germ extracts, it was possible to produce a CFPSS that supported co-translational myristoylation of Gag and its targeting to endogenous membrane surfaces, and achieve *de novo* immature HIV-1 capsid assembly (39). Authenticity of immature capsids assembled in the CFPSS was supported by several criteria, including sedimentation value, buoyant density and EM appearance (compared to immature capsids produced in transfected mammalian cells). Furthermore, in this cell-free system, HIV-1 capsid formation failed to occur in the absence of co-translational myristoylation or if membrane integrity was abolished (39).

Having demonstrated formation of immature HIV-1 capsid in a manner that appears faithful to the product in cells, this system was utilized to ex-

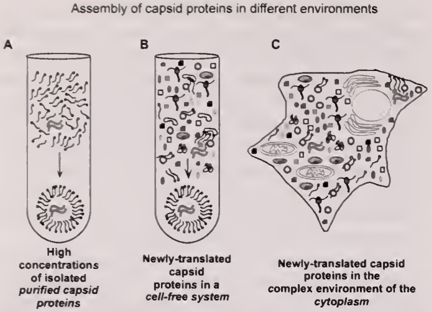
Assembly of capsid proteins in different environments
A
B
C
High concentrations of isolated *purified capsid proteins*
Newly-translated capsid proteins in a *cell-free system*
Newly-translated capsid proteins in the complex environment of the *cytoplasm*

Fig. 6. Assembly of HIV-1 capsid proteins in different environments. (**A**) Early studies of HIV-1 capsid assembly were performed using high concentrations of purified capsid proteins in isolation from cellular proteins and organelles. These studies revealed that capsid proteins have an intrinsic ability to self-assemble, but failed to give us insight into how capsid assembly occurs efficiently in the complex environment of the cell. (**B**) CFPSS were used to reconstitute HIV-1 capsid assembly by linking synthesis of capsid proteins to post-translational events of assembly in the presence of the high concentration of cellular protein as well as organelles. Thus, in contrast to self-assembly systems (A), the HIV-1 capsid assembly CFPSS (B) mimics many features of the HIV-1 assembly process that occurs in cells (**C**).

amine the mechanism of capsid formation. Pulse-chase experiments revealed that newly synthesized Gag polypeptides progress sequentially through a series of novel post-translational complexes of defined sizes (10S, 80S, 150S, and 500S) before culminating in formation of completed 750S immature capsids. Confirmation that these complexes are *bona fide* assembly intermediates came from the demonstration that assembly defective mutants in Gag, defined by others using cellular systems, were arrested at specific points in this assembly pathway, producing for each class of mutant, a subset of the same assembly intermediates that were observed for the wild type capsid protein in the CFPSS (39). In contrast, Gag mutants that were known to be assembly competent progressed through each of the assembly intermediates to the final 750S completed immature capsid (91).

Each of the key features of CFPSS indicated above (near the end of the first section) are illustrated in the studies analyzing viral capsid assembly. First, the fidelity of CFPSS in reproducing the capsid assembly pathway that occurs in cells has been confirmed by recent studies identifying capsid assembly intermediates in mammalian cells producing HIV-1 and other primate lentiviral capsids (36). Second, assembly intermediates are extremely transient, rapidly progressing, and are present in very low steady-state quantities in mammalian cells. This explains why they had not been noticed before: by standard techniques; the signal-to-noise ratio was not sufficient to distinguish them from background. These assembly intermediates were first identified in a CFPSS because these systems reproduce events more slowly and inefficiently than do cells, as discussed above, allowing accumulation of these transient complexes to levels that were easily detectable. Third, since the CFPSS was programmed only with mRNA-encoding Gag polypeptide, resulting in synthesis and post-translational modification of Gag, the presence of the observed assembly intermediates could be attributed to capsid assembly. If they had been found first in the context and complexity of a cell, their relevance to capsid assembly would not have been obvious. Thus, identification of capsid assembly intermediates is an example of how the cell-free system can be a better model than living cells for initial dissection of complex biological systems. Of course, ultimately, these conclusions must be corroborated *in vivo*, as has been done for capsid assembly intermediates (37), but this is best done with a "heads up" as to what to look for, by virtue of studies of CFPSS.

The fourth advantage of CFPSS (as listed above) is that they provide the opportunity for manipulations that would be difficult to perform *in vivo*. This was illustrated by subsequent studies in which energy dependence was localized to the 80/150S step in the ordered pathway of assembly intermediates. The energy dependence was demonstrated by treating extracts *post-translationally* with an enzyme (apyrase) that hydrolyzes adenosine triphosphate (ATP) (39). While studies of ATP depletion can be performed in cells, its effects cannot easily be localized in time or space within a cell; this was achieved in the CFPSS. Since energy-utilization is a common hallmark of biological regulation, the observation of energy dependence during post-translational events in HIV-1 capsid assembly was crucial for overturning the notion that capsids self-assemble in cells, which was the dominant view at the time. Furthermore, this observation had important implications with respect to viral-host interactions. Since Gag does not contain ATP-binding domains, and Gag is the only viral protein programmed into the cell-free HIV-1 capsid assembly system, the requirement for ATP hydrolysis suggested that a cellular ATP-binding protein was needed for HIV-1 capsids to assemble.

The existence of a cellular factor required for HIV-1 capsid assembly had been indicated by previous fractionation and reconstitution data (39), illustrating the fifth advantage of CFPSS. Such an approach would not be possible in living cells. Together, these findings led to the search for a host factor critical for assembly, and resulted in identification of HP68 (also known as RNAse L inhibitor), a cellular protein that contains two ATP-binding domains. HP68 was identified because it associates with 80S, 150S and 500S assembly intermediates, but not with completed 750S immature capsids in the CFPSS. In support of the fidelity of CFPSS, this association is also seen in transfected and infected primate cells (37, 92). The association of HP68 with Gag polypeptides in the assembly intermediates, but not the completed capsid, suggests that it plays a catalytic role in assembly analogous to that of enzymes in a biochemical pathway or of molecular chaperones in protein folding. It is puzzling why a protein that serves as a ribonuclease inhibitor should also facilitate building a viral capsid. Given this and other mysteries that surround the action of host factors involved in viral capsid assembly, the term "molecular facilitators" has been coined to distinguish them from conventional molecular chaperones, whose actions may or may not be similar.

Depletion and reconstitution in the CFPSS was used to determine whether HP68 is required for HIV capsid assembly. Immunodepletion of HP68 from the CFPSS resulted in an extract that supports near-normal levels of HIV-1 Gag synthesis but no longer allows efficient formation of 750S completed capsids. Presumably, the small amount of residual assembly observed in depleted extracts reflected the catalytic action of residual HP68. When recombinant purified HP68 was added back to the immunodepleted CFPSS extract, efficient 750S capsid assembly was reconstituted, supporting an essential role for HP68 in capsid formation. These findings were corroborated in living cells by demonstrating that dominant negative mutants of HP68 *blocked* release of HIV from transfected mammalian cells and HIV-infected human T cells (92).

Subsequently, other groups have confirmed the role of ATP in retrovirus assembly using cellular systems (93–95). However, since these studies did not distinguish between use of energy for capsid protein synthesis versus post-translation events in capsid assembly, we designed another approach to confirm the existence of an energy-sensitive step in capsid assembly in cells. We demonstrated that when extracts of primate cells expressing the nearly complete HIV-1 genome were harvested in the presence of ATP, the energy-dependent 80S and 150S complexes were present in minuscule quantities, suggesting that Gag polypeptides progress rapidly through these complexes when energy is not limiting. However, when harvested under ATP-depleted conditions, all of the Gag-containing post-translational assembly intermediates we had identified in the cell-free system could be seen biochemically. The assembly intermediates that were found in the cell-free system fit the criteria previously defined for these complexes in the CFPSS. That is, they contained HP68 associated with Gag only in the 80S, 150S, and 500S complexes, and were not associated with Gag in unassembled 10S complexes or in the fully completed 750S capsids (37). Finally, these studies in cells allowed us to extend findings obtained for HIV-1 assembly to other members of the family Lentiviridae. Genetically divergent primate lentiviruses from 3 separate lineages all appear to utilize the HP68 and ATP-dependent, stepwise assembly pathway for immature capsid assembly (Fig. 7) when expressed in cells (37). Further cellular studies and, ultimately, animal studies will be important for confirming the accuracy of observations initially made in CFPSS.

Through studies of HBV and HIV capsid formation, the CFPSS has given us a radically different view of how viral capsids assemble. In this new view, the conceptual framework of self-assembly has been replaced by a cell-biological paradigm involving a stepwise, ordered biochemical *pathway* for capsid formation, characterized by discrete intermediates, energy and subcellular

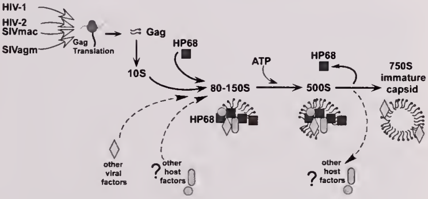

Fig. 7. Immature primate lentivirus capsids assemble in an energy-dependent manner by a pathway of assembly intermediates containing the cellular factor HP68. Studies in CFPSS followed by confirmatory studies in cellular systems have revealed that HIV-1 assembles capsids by sending newly synthesized viral Gag polypeptides through a sequential pathway of assembly intermediate complexes identified by their sedimentation values (10S, 80–150S, and 500S). Other primate lentiviruses, including human immunodeficiency virus type 2 (HIV-2) and strains of simian immunodeficiency virus that infect African green monkeys (SIVagm) and macaques (SIVmac), also utilize this assembly pathway. In the 80–150S assembly intermediate, Gag polypeptides become associated with the host protein HP68. HP68 remains associated with the nascent virion until just before completion of the 750S immature capsid structure. HP68 has been shown by two methods to be essential for completion of capsid assembly. Other viral proteins present in completed virions are also found in assembly intermediates and recent studies suggest that other cellular factors may be present as well.

compartment-specific steps, and engagement of host proteins serving as catalysts or *molecular facilitators*. The role of such molecular facilitators in assembly may be similar to that of enzymes that serve to speed up chemical reactions that would occur spontaneously to a small extent in the absence of the enzymatic facilitator. There is now ample evidence for the existence of the same facilitated, energy-dependent assembly pathways in cells assembling primate lentiviruses. However, finding these assembly intermediates in cells would have been extremely difficult without the road map made available by studies in CFPSS, which facilitate detection of transient and complex post-translational regulatory events that are tightly linked to protein synthesis.

The Biogenesis of Complex Proteins at the ER

Translocation across the ER membrane provided an important focus for the original development of the modern CFPSS. Therefore, it should not be surprising that this system has contributed significantly to our current understanding of complex protein biogenesis at the ER. Some of these insights are summarized below.

Prion Protein

The prion protein (PrP) is a widely expressed glycoprotein which has been implicated in an extraordinary group of neurodegenerative disorders, some of which are transmissible, and others hereditary; still others occur sporadically in the absence of either family or exposure history (96). Initially, a distinction was made between "normal" PrP, i.e., that observed in uninfected cells (PrP^C) and the form observed in infectious prion disease (PrP^{Sc}) (97). Infectious prion disease involves conversion of PrP^C into PrP^{Sc}, an abnormally folded form that triggers neurodegeneration and, upon entry into cells, converts endogenous PrP^C into more PrP^{Sc}, thereby conferring the "infectious" character that is a hallmark of these disorders. Until recently, the normal function of PrP (PrP^C) has been quite controversial. Some data has suggested that it is involved in apoptosis (98). Other data has argued for a neuroprotective function (99). Subsequent work suggests a far greater complexity and heterogeneity of what had been termed PrP^C, which sets the stage to better understand previously mysterious features of prion disease (38, 44).

Studies of the CFPSS have contributed greatly to our current understanding of PrP physiology and pathophysiology. Upon expression in CFPSS, an initially *homogeneous* population of nascent PrP chains is completed as a *heterogeneous* mix of three forms (termed "conformers"), identical in primary amino acid sequence, but distinctive in transmembrane topology and final folded state (38). That these forms are different in transmembrane topology can be demonstrated unambiguously by digestion with proteinase K (PK) under harsh conditions with membranes intact (Fig. 8A). However, upon digestion with PK under mild conditions, in the absence of membrane integrity, it is possible to distinguish intrinsic differences in PrP conformer folding (Fig. 8B). One form, termed ^{Ctm}PrP, spans the membrane with its N terminal half in the cytoplasm and is intrinsically protease resistant. That is, upon solubilization of the ER membrane with nondenaturing detergents (i.e., which do not disturb protein folding), a "signature" mild PK digestion-resistant peptide fragment remains. Another form is termed ^{Sec}PrP, because the region that spans the membrane in ^{Ctm}PrP is fully translocated to the ER lumen in the CFPSS. *In vivo,* mature ^{Sec}PrP is found anchored to glycolipids on the cell surface. ^{Sec}PrP shows no protease resistance once membranes are solubilized with nondenaturing detergents. A third form, termed ^{Ntm}PrP, spans the membrane with carboxy terminus in the cytoplasm, and, like ^{Sec}PrP, shows no PK resistance, even with mild PK conditions, when membrane integrity is abolished. The significance of ^{Ntm}PrP is unknown, although some have claimed to detect it *in vivo* (100). Fig. 8C illustrates how the CFPSS allows these forms to be detected (contrast this with Fig. 2B). Until these studies, it had not been possible to resolve PrP^C into its three component conformers, and so, the possibility that different conformers are responsible for different subsets of the functions previously ascribed to PrP^C, could not be appreciated. *In vivo* PrP heterogeneity is bewildering, with differentially glycosylated forms (e.g., utilizing either, both or none of the two available N-glycosylation acceptor sites), and endogenous proteolytic metabolic cleavage products (101), complicating the analysis and making it harder to resolve conformer distinctions that are seen clearly in the CFPSS.

The pathophysiological significance of PrP conformer heterogeneity was clarified in a series of studies (27, 38). First, the CFPSS was used to screen for mutations that skewed the distribution of PrP towards either ^{Ctm}PrP or ^{Sec}PrP. Such mutations were found and introduced as transgenes into a null background (i.e., into mice whose endogenous PrP gene had been deleted by homologous recombination). Those mice with transgenes favoring ^{Ctm}PrP developed rapid spontaneous neurodegeneration with spongiform change and astroglio-

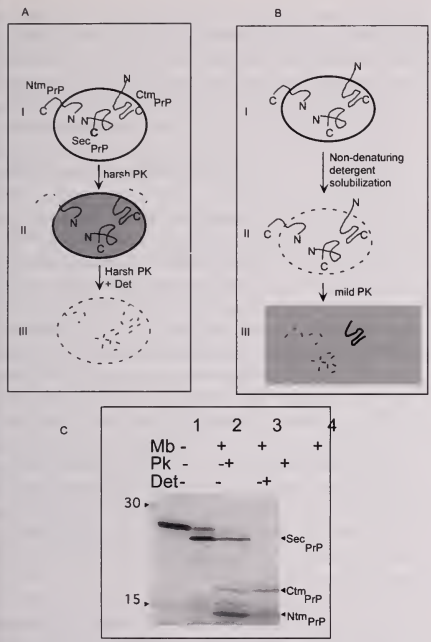

Fig. 8. Assays of protein prion (PrP) biogenesis in CFPSS. **(A)** Topological assay. Harsh proteolysis with PK with intact membrane vesicles removes domains outside the bilayer only (panel II). Membrane solubilization with nondenaturing detergent (Det) abolishes topological differences, so that all forms are degraded. **(B)** Conformational assay. Mild proteolysis with PK, with intact membranes vesicles, gives the same result as in the harsh protease topological assay. Solubilization of the membrane with nondenaturing detergent abolishes topological differences (panel II), but not differences in conformation. Thus, mild protease digestion under these conditions demonstrates intrinsic differences in folded state by protection of a signature fragment of ^{Ctm}PrP (panel III). **(C)** Analysis of PrP biogenesis in cell-free translation systems with mild proteolysis, followed by SDS-PAGE and autoradiography (AR). Lanes 1–3 demonstrate the topological assay, displaying PrP synthesis in the absence of microsomal membranes (Lane 1), synthesis in their presence (lane 2) and after PK digestion (Lane 3). Lane 4, the conformational assay, involves solubilization of the protecting lipid bilayer so that the protein is fully accessible to PK. However, since PK digestion conditions used were "mild" conditions under which one conformer is fully digested (^{Sec}PrP), while another conformer, ^{Ctm}PrP, displays a signature protease-resistant fragment.

C = carboxyterminal; N = N terminal; Sec = secretory, and Mb = membrane.

sis, the pathological hallmarks of prion disease, and were found to have ^{Ctm}PrP in their brains, but no PrP^{Sc} (27). Furthermore, the brains of these sick mice did *not* transmit prion disease when inoculated into healthy mice. Thus, infectivity and pathogenicity in prion disease appear distinct. Some of the mutations that favor ^{Ctm}PrP are found in patients with Gerstmann-Straussler-Sheinker (GSS) syndrome, a hereditary dementia. Studies of patients with GSS revealed the presence of ^{Ctm}PrP in their brain stissue. Mice with those transgenes developed spontaneous neurodegeneration, again without PrP^{Sc}, and without transmissibility to other animals.

Those mice with transgenes favoring ^{Sec}PrP developed no spontaneous disease and were found to be protected from infectious prion disease. Upon inoculation with infectious prions, they developed disease very late and only after enormous levels of PrP^{Sc} had accumulated. ^{Sec}PrP is the only mature conformer of PrP observed at steady state in normal adult brains of both humans and wild type PrP transgenic (wtPrP Tg) mice. A body of work (27) suggests that ^{Sec}PrP is the conformer of PrP that is the substrate for production of PrP^{Sc}. A cell culture system that reproduces the conformer distribution achieved in CFPSS supports the notion that ^{Sec}PrP has a physiological function antagonistic to that of ^{Ctm}PrP. Thus, Chinese hamster ovary (CHO) cells transfected with ^{Sec}PrP-favoring mutants appear *protected* from various forms of apoptosis (Saghafi et al., unpublished).

Finally, ^{Ctm}PrP has been implicated in the signaling pathway by which PrP^{Sc} causes neurodegeneration in infectious prion disease, by two independent lines of evidence. First, a striking correlation is observed between the propensity of a mutation to favor ^{Ctm}PrP in the CFPSS, adjusted for the level of expression in a particular Tg line (termed the Ctm-index), and the level of accumulation of PrP^{Sc} at time of onset of clinical disease, after inoculation with scrapie (27). Together with other data, these findings suggest the following hypotheses:

- ^{Ctm}PrP allows the cell to monitor the level of PrP^{Sc} and responds to PrP^{Sc} accumulation by triggering apoptosis;

- PrP^{Sc} inactivates pathways that normally suppress ^{Ctm}PrP expression. In this view, cells expressing ^{Ctm}PrP-favoring PrP mutations have elevated levels of nascent ^{Ctm}PrP and therefore are already closer to the threshold level of ^{Ctm}PrP needed to exit the ER and trigger apoptosis, even prior to inoculation with PrP^{Sc}. Upon inoculation, PrP^{Sc} replication triggers ^{Ctm}PrP export from the ER. Thus, a smaller amount of PrP^{Sc} is needed to reach that threshold in the case of Tg lines expressing ^{Ctm}PrP-favoring mutations.

These hypotheses and observations allowed formulation of a hypothesis to relate the different categories of prion disease and clarify the distinction between the events of *transmission* and the separate events of *disease pathogenesis* (see Fig. 9, stage I vs. stage II/III).

A body of work has clarified some of the molecular mechanisms by which different PrP conformers are made at the ER. First microsomal membranes were solubilized, fractionated and reconstituted with the few gene products absolutely needed for translocation across the ER (SRP receptor; Sec61p; and in some cases, TRAM). When wtPrP is synthesized in the presence of these membranes, ^{Ctm}PrP is the only conformer observed (44). Addition of a glycoprotein fraction reconstitutes formation of the ^{Sec}PrP conformer, upon wtPrP translation (44). Subsequent work has identified translocon-associated protein (TRAP) alpha as a component of the glycoprotein complex needed to make ^{Sec}PrP (103). Since ^{Sec}PrP may have a role in protection from apoptosis and ^{Ctm}PrP appears to be a trigger of apoptosis (Saghafi et al., unpublished), this ER membrane glycoprotein complex is a "protective" factor that prevents apoptosis by redirecting the nascent PrP chain away from the default pathway leading to the formation of ^{Ctm}PrP (44). Other data from our lab suggest that at particular times in development, ^{Ctm}PrP is induced in order to trigger physiological apoptosis (V. Lingappa, unpublished). Thus, prion disease appears to be a case in which a physiological mechanism (triggering of apoptosis by ^{Ctm}PrP) is activated at an inappropriate time and/or place.

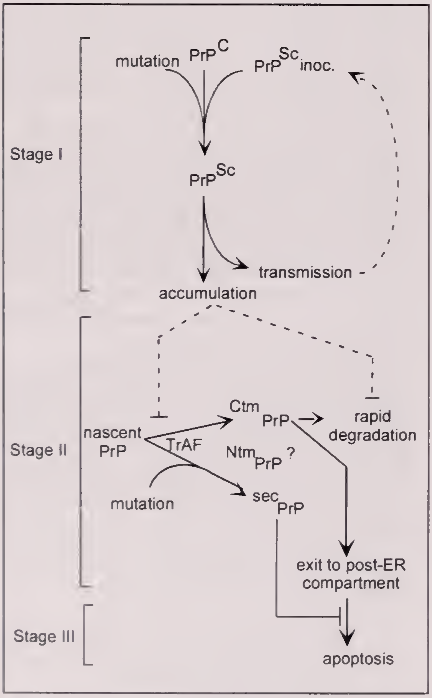

Fig. 9. Steps in prion protein pathogenesis. Relationship of infectious cycle (stage I) to pathway of *de novo* PrP biogenesis (stage II) to pathway of apoptosis (stage III), copied with permission from Hegde RS, Tremblay P, Groth D, et al. Transmissible and genetic prion diseases share a common pathway of neurodegeneration. Nature 1999; 402(6763):822–826 (27). The three conformers that comprise what was previously known as PrP^C were first identified in CFPSS. This proposal also accounts for how a point mutation of PrP can result in spontaneous neurodegeneration (by favoring ^{Ctm}PrP production and activation of apoptosis), without generation of infectious PrP^{Sc}, which is necessary for spread of transmissible prion disease.

TrAF = translocation accessory factor.

When a mutation that is expressed only as ^{Sec}PrP was translated in the presence of minimal membranes (which make only ^{Ctm}PrP), the chains were found to target but not translocate across the ER membrane (44). These studies of PrP biogenesis suggested the existence of *multiple pathways* across the ER membrane, and that the correct fit between translocation substrate and accessible pathway is necessary, if the chain is to be faithfully translocated. The mutation in question appears to prevent the PrP chain from accessing the pathway utilized to form ^{Ctm}PrP, and the minimum membranes are missing the factor needed to establish the pathway utilized to form ^{Sec}PrP. Subsequent studies have reinforced this conclusion (72, 104–106, and Ott and Lingappa unpublished).

The studies to date on PrP have highlighted the power of the CFPSS (Table): ^{Ctm}PrP was first detected in the CFPSS but later confirmed by studies in Tg mice; whereas ^{Ctm}PrP is difficult to detect *in vivo* at steady state in the adult, it is readily detected in the CFPSS, because only a subset of events occurring *in vivo* are reconstituted under standard conditions in the CFPSS (e.g., ER degradation is not). Mutations expressed in the CFPSS have clarified some aspects of PrP biogenesis (104–106), and manipulations in *trans* (fractionation and reconstitution) (44, 103).

CFPSS have not only allowed recognition of conformational heterogeneity in the initial products of PrP biogenesis, but have also allowed this phenomenon to be appreciated in a more measured fashion than would have been possible *in vivo,* where the bewildering plethora of diverse modified forms that constitutes heterogeneity of PrP is more daunting.

Protein Bioconformatics

Initially, the evidence for alternate folded forms, or conformers, for PrP in the CFPSS was interpreted as revealing an unusual feature of PrP biology. However, a growing body of evidence suggests that the conformational heterogeneity observed for PrP is *not* unique or even unusual, and may well be a widespread property of secretory, membrane, and even cytosolic proteins. The seminal observation in favor of this radical new view was that replacing the signal sequence of PrP with that of a variety of different simple secretory proteins such as prolactin and immunoglobulin heavy chain, resulted in dramatic changes in the ratio of ^{Sec}PrP to ^{Ctm}PrP upon synthesis in the CFPSS (106). If the signal sequence's role is simply to target to the ER and translocate, then why should there be the observed correlation of specific signal sequences with the generation of a particular mix of conformers? The subsequent discovery that different PrP conformers have dramatically different functions (^{Ctm}PrP triggers apoptosis in transfected cells, ^{Sec}PrP protects transfected cells from apoptosis and oxidative stress, Saghafi et al., unpublished) suggests that this observation is significant and raises some interesting possibilities.

One possibility is that the signal sequence plays a role beyond targeting to, and translocation across, the ER membrane *per se*. Specifically, the signal sequence appears to be a critical determinant of the *pathway* across the ER membrane. Hence the variation long noted between signal sequences might be *functional*, used as a means of fine-tuning the folding pathway to be taken by the nascent chain. That is, rather than variations between signal sequences reflecting the *lack* of specific information restricting their divergence, these variations may reflect the fact that different proteins have *selected* mutations of the signal sequence that access the particular mix of folding funnels desired by the cell for that particular protein. Such selection would be complex, occurring in concert with degradative and other mechanisms that allow the cell to "sculpt" the mix of conformers generated, in response to physiological or other cues.

The second implication of this observation is that perhaps what is unusual about PrP is not that it is made in multiple conformers, but rather that those conformers are *easy to detect because they manifest as differences in topology*, which are far easier to score than subsets of chains of different conformation. A study of proteins other than PrP has now explored this hypothesis and suggests that it may be more generally correct, and that multiple mechanisms exist by which conformational hetero-

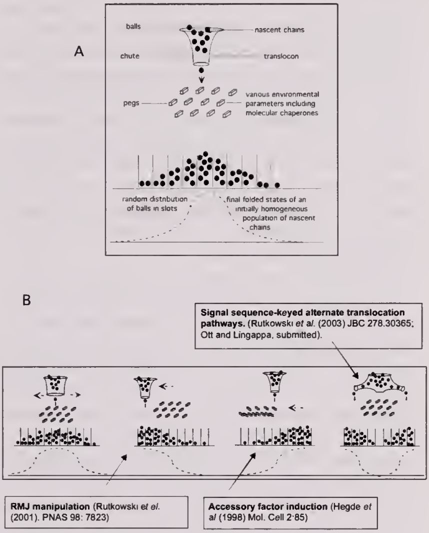
A
balls
nascent chains
chute
translocon
pegs
various environmental parameters including molecular chaperones
random distribution of balls in slots
final folded states of an initially homogeneous population of nascent chains
B
Signal sequence-keyed alternate translocation pathways. (Rutkowski et al. (2003) JBC 278.30365; Ott and Lingappa, submitted).
RMJ manipulation (Rutkowski et el. (2001). PNAS 98: 7823)
Accessory factor induction (Hegde et al (1998) Mol. Cell 2·85)

Fig. 10. Protein bioconformatics. (A) Analogy to protein folding through the translocon. The balls represent nascent chains, the chute represents the translocon, the pegs represent molecular chaperones and environmental parameters that alter protein-protein interactions between the nascent chain and translocon, and the slots at the bottom of the figure represent the diverse final folding states that achieve relative energy minima to which the chain can be directed, and into which the balls ultimately distribute. **(B)** The conformational distribution can be changed by manipulating one or more of several (separately regulated) parameters, including the accessible environment (e.g., cytosol vs. lumenal), as a consequence of open vs. closed ribosome-membrane junctions, specific protein-protein interactions during the course of translocation, timing of events and modifications, and pathways out of the translocon. Over the course of evolution, the necessary "waste" of energy for synthesis of chains that achieve alternate conformations undergoes selection for particular purposes. In some cases, evolution may have closed off certain pathways by selecting signal sequences that do not allow the chain access to those folding funnels. In other cases, contingency was maintained perhaps by coupling to signaling cascades, so that one pathway or another was accessible at different times (e.g., in response to phosphorylation of particular trans-acting proteins). PrP biogenesis is probably an example of the latter. Note that evidence has been generated for three of the hypothetical examples of regulation indicated; see references 72 and 106.

geneity can be regulated in response to the physiological needs of the cell (Fig. 10) (72). One such mechanism appears to involve the RMJ. Long thought to form a tight seal between the secretory ribosome and the ER membrane, it has been observed that in some cases an open RMJ is established, while under other circumstances a closed RMJ is formed. When the RMJ is open, specific information later in the chain seems capable of effecting RMJ closure. When the RMJ is closed, specific information later in the chain can direct its opening. Opening and closing of the RMJ appears to be achievable either by discrete sequences in the mature chain, termed pause transfer sequences (42, 71), or by different classes of signal sequences themselves (106). Thus, while all signal sequences seem to direct their "passenger" nascent chains to the ER membrane, the precise *pathway* across the membrane (via the translocon) that is achieved depends, in part, on which class of signal sequence the protein has evolved.

Classes of signal sequences appear to differ in ways beyond the characteristics of the RMJ they establish. In a case where two signal sequence affect folding of two unrelated proteins (prolactin and TIGR) *without* opening the RMJ, a change in organization of the translocon (as demonstrated by chemical cross-linking to a truncated nascent chain in the CFPSS), has been correlated with each outcome (72). However, it remains to be determined whether these two forms of conformational regulation are truly different mechanisms, or whether they may represent different manifestations of a more limited set of mechanisms. Finally, factors such as TRAP alpha, an integral membrane glycoprotein, have been implicated in redirecting nascent chains in *trans* (103). For some of these mechanisms (e.g., regulation of the RMJ) there may be multiple sub-states (e.g., closed vs. partially open vs. largely open vs. completely open), rather than simply open vs. closed RMJs. In other cases, there may be a number of pathways through the translocon. In still other cases, there may be *trans*-acting factors in the cytoplasm, the ER membrane or the ER lumen. Each of these mechanisms may be keyed by different classes of sequences, encoded in different classes of proteins. In some cases, signal sequences play this role. Possibly, a hierarchy of such mechanisms is activated as a nascent chain progresses across the ER membrane, closing off some folding funnels while opening others, in the course of chain growth and translocation.

A third implication of the signal sequence swapping experiments is that seemingly subtle mutations in a signal sequence can have dramatic effects on the folding of the nascent chain "passenger." Thus, the conventional view that signal sequences of different proteins display many small changes in precise amino acid sequence because they are relatively nonspecific in their function should be turned on its head: the precise sequence of the signal peptide has been tailored to direct the passenger to the precise mix of final folded states selected over the course of evolution. Further work is needed to corroborate or refute this new view of signal sequence heterogeneity.

Multispanning Membrane Proteins

It is remarkable that swapping seemingly "simple" signal sequences from different secretory proteins affects the folding of the passenger nascent chain, even though the signal sequence is (eventually) cleaved. Whether the notion of protein bioconformatics growing out of this observation is generally applicable to most proteins or applies only to a small subset of secretory and membrane proteins, awaits further experimental investigation. Nevertheless, it is most tempting to apply the concept to biogenesis and folding of multispanning membrane proteins, where one might expect a great potential for heterogeneity in conformation/topology to expand the information content expressed in a gene product. However, these proteins are exceedingly difficult to study, and few studies have been carried out with precision to distinguish conformations/topological forms under conditions not confounded by rapid degradation in the ER. Here again lies an advantage of analysis in CFPSS.

In one case, that of multidrug resistance gene-1 (MDR-1), a striking finding highly analogous to the observations on PrP biogenesis has been made (107). It was found that this multi-spanning membrane protein, predicted to be made as two sets of six-membrane spanning loops, had a previously unanticipated degree of heterogeneity at loops 7–8. A little more than half of the chains had this sequence in the orientation expected (i.e., forming two transmembrane loops). However approximately 40% of the chains had the entire region localized to the ER lumen, in a manner reminiscent of PrP topological heterogeneity (see Fig. 11). This raises the possibility that certain membrane proteins utilize mechanisms similar to PrP to achieve different conformation/topology for different subsets of chains. Each of these subsets of chains of different conformation or topology may serve different functions in a manner that is extremely difficult to detect, let alone follow, *in vivo*.

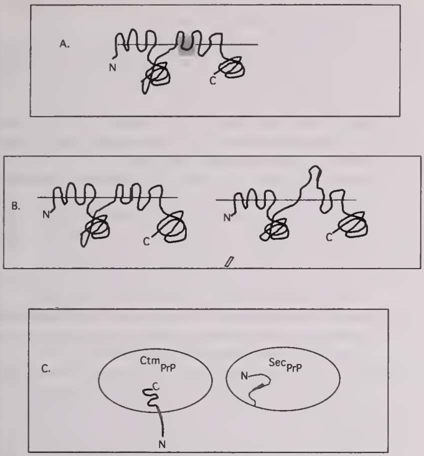

Fig. 11. Multispanning membrane protein heterogeneity. Summary of data from reference 107. **(A)** Predicted topology of multidrug resistance gene-1 (MDR-1), a multispanning integral membrane protein of the ABC transporter superfamily. **(B)** Experimentally demonstrated mix of topological forms observed first in the CFPSS (107). **(C)** Similarity in local orientation of transmembrane loops of MDR-1 to topological heterogeneity of PrP, suggesting that common mechanisms may be at work.

Anticipating Future Developments

It is possible that cytoplasmic proteins with no relationship to the ER also have sequences that, by association with trans-acting factors such as molecular facilitators, redirect the folding of nascent proteins. If activity of these *trans*-acting factors is entrained by signaling pathways, it becomes possible to induce a particular conformer in response to metabolic, developmental or cell type and tissue-specific circumstances. While some of these interactions may be disease, tissue, or cell-type specific, others may be more general and occur in CFPSS, as is true for redirecting nascent chains of PrP to ^{Sec}PrP vs. ^{Ctm}PrP, which will facilitate their detection and elucidation.

The complex cell-biology sleuthing in the CFPSS summarized above is still in progress, both for cytoplasmic proteins like HP68 and viral capsid proteins, and for secretory and membrane proteins like PrP, prolactin and MDR-1 and others. The full implications of the findings discussed here remain to be established. At the very least, they represent important variations on the theme of protein biogenesis, which need to be understood for a full appreciation of human disease and biological diversity. In the broadest extrapolation, they represent a new way of thinking about protein folding and its regulation—protein bioconformatics. The studies of viral capsid assembly and protein bioconformatics discussed above amply illustrate the power of the CFPSS to jump start new lines of inquiry with respect to the mechanism by which these extraordinary biological regulatory events occur.

Recent findings suggest that CFPSS have a high potential for revealing other remarkable levels of biological regulation that were previously not anticipated. Thus, CFPSS have been instrumental in revealing that the steroidogenic acute regulatory (StAR) protein, whose activity is the rate-limiting step in steroidogenesis, and which is localized to the mitochondria matrix, carries out its biological function at the outer mitochondrial membrane. How it could work at a location other than that in which it was found was clarified by CFPSS studies that reconstituted StAR function and manipulated the signals for its biogenesis in a manner that revealed its novel mode of regulation (77). Likewise, the recent demonstration that the proximal and distal limbs of the secretory pathway probably "talk" to one another as part of a regulatory feedback loop engaged during specific protein synthesis (108) suggests still more aspects of biological regulation that the CFPSS may help decipher. Will CFPSS deliver fully on the promise suggested by these studies? Time will tell.

Summary and Conclusions

We have presented a very different way of viewing CFPSS that is in continuity with the history of cell biology and biochemistry. We have showcased in detail two dramatic examples where use of CFPSS is ushering in new paradigms of thinking, first in viral capsid formation, and second, growing out of the study of prion protein biogenesis and leading to the theory of protein bioconformatics. We hope that the "take-home message" will be an appreciation of the power and still-to-be-tapped richness of this approach to complex issues in biology. In addition, we hope that the reader will be challenged to apply these systems to other topics in biology that are connected to protein synthesis but where the answers have been taken for granted. This is particularly true where some data already suggests a degree of complexity not addressed by simpler models. In such cases, the CFPSS may provide important and unexpected answers that must eventually be validated *in vivo*.

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The Rational Use of Dietary Supplements and Nutraceuticals in Clinical Medicine

JEFFREY I. MECHANICK, M.D.

Abstract

The rational use of dietary supplements and nutraceuticals (DS/N) is based on objective evaluation of the clinical evidence as well as subjective evaluation of the risks, benefits, economic costs, and potential drug interactions. Since the use of DS/N has skyrocketed, physicians must learn about them in order to better communicate with and care for their patients. There are many evidence-based and rational uses for DS/N, but profiteering and quackery must be avoided at all costs.

Key Words: Dietary supplements, nutraceuticals, alternative care.

Introduction

THE PRACTICE OF CLINICAL MEDICINE spans a range of methodologies from disciplined scientific investigation to an impressionistic system of health care. Creative solutions to clinical problems incorporate subjective, humanistic qualities that cannot always be scientifically tested. However, the advocacy of unproven therapies, heralded as standards of care or appropriate interventions, cannot be condoned. Such is the case for many of the published indications for dietary supplements and nutraceuticals (DS/N) and their seemingly widespread recommendation for a host of ailments. The purpose of this article is to present a framework for the rational, safe and beneficial use of DS/N. A technical review of the data supporting or refuting the use of specific DS/N is beyond the scope of this article, but may be found in the American Association of Clinical Endocrinologists' Clinical Practice Guidelines on the topic (1).

Defining the Problem

Several key concepts need to be defined first. The practice of medicine that strays from the basic tenets taught in American medical schools is termed "alternative," "complementary," "unconventional," "integrative" or "holistic." This paradigm incorporates two other features: (a) addressing symptoms rather than diagnoses of diseases and (b) relying on lesser levels of scientific substantiation or none at all, i.e., anecdote and testimonial. One of the major problems of this second feature is that the "placebo-effect" can clearly account for purported benefits. The major issue is not whether these alternative medical practices are "right" or "wrong," but rather whether they cause harm. This issue is difficult to address, because the line between traditional standards of care and quackery is blurred.

Why is alternative care popular? People become disenchanted with the medical profession and flock to alternative medicine when complaints, such as pain or fatigue, cannot be adequately treated, or diseases, such as certain forms of cancer, cannot be cured. In addition, alternative care is promoted by the media, especially over the Internet, which is an ever-increasing source of health care advice and information. An impetus for the promotion by the media is the profit motive. The public may seek traditional medicines when they are *sick*, but they also seek DS/N when they want

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Director, Metabolic Support, Associate Clinical Professor of Medicine, Division of Endocrinology, Diabetes and Bone Diseases, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Jeffrey I. Mechanick, M.D., 1192 Park Avenue, New York, NY 10128; email: jmechanick@aol.com

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to *promote health*. To some extent, many people use DS/N to self-treat, almost as if they are personally challenging the traditional medical system. Alternative care practitioners and their customers promulgate the concept that *natural* products are superior to and safer than *synthetic* products or *drugs*. This distinction, in the context of treating disease states, is not based on scientific data and may be viewed as irrational.

Many DS/N advertisements lead the public to believe that the scientific evidence for the efficacy of the product is comparable to that required for FDA-approved drugs, when in fact the DS/N data are clearly inferior. In addition, advocates of alternative care use medical pseudojargon and elaborate physiologic theory very persuasively. Moreover, patients can become confused when the distinction between traditional and alternative care becomes blurred: some traditional doctors prescribe pharmaceuticals to treat diseases in ways that are unproven (e.g., statins for osteoporosis) and they also prescribe DS/N to treat diseases in ways that are proven (e.g., calcium and vitamin D for osteoporosis). However, to be fair, if patients are not receiving successful treatments using the traditional route, and if they seek an alternative care approach that is relatively harmless, regardless of benefit, and if the cost for these interventions is fair and not exploitative, then the practice of alternative medicine can be potentially valuable. The problem is the "ifs."

For years, the Food and Drug Administration (FDA) required extensive paperwork from manufacturers that was seen by some as impeding the prompt availability of DS/N to the general public. In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA) to facilitate the investigation and appropriate use of DS/N (Table 1). However, despite these regulations, tremendous qualitative and quantitative variability exists in the composition of DS/N products.

Nutraceuticals have been defined as dietary supplements that contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a nonfood matrix, and used to enhance health in dosages exceeding those obtainable from normal foods (2). Examples would be vitamin supplements, ipriflavone tablets for osteoporosis or fish-oil capsules for lipid disorders. To be more precise, perhaps, the term "*nutra*-ceuticals" refers to compounds containing many bioactive substances, not necessarily nutrients, targeting multiple physiologic actions with many "healing effects" and "*nutri*-ceuticals" refers to compounds containing one nutrient promoting one healing effect (3). *Functional foods* are foods and beverages with claimed health benefits based on scientific evidence. For simplicity, in this review, "DS/N" refers to dietary supplements, nutraceuticals, nutriceuticals, and functional foods (Figure).

TABLE 1
Features of the Dietary Supplement Health and Education Act (DSHEA)

Authorizes increased funding for the Office of Alternative Medicine at the National Institutes of Health.
Provides for increased investigations of DS/N by the Cochrane-Controlled Trials Register.
Defines dietary supplements as:
- a vitamin or mineral
- an herb or other phytochemical
- an amino acid
- a dietary substance to supplement the diet by increasing the total dietary intake (e.g., enzymes, organ tissue or glandular tissue)
- a concentrate, metabolite, constituent or extract of any of the above
- not foods in their natural form
- not meal substitutes like Ensure® or Boost®

Permits 3 types of claims on labels:
- nutrient-content ("high in calcium")
- structure-function or nutrition support ("calcium builds strong bones")
- disease-treatment claims ("calcium treats osteoporosis")—must have FDA authorization based on scientific data

Allows the FDA to monitor adverse reports, issues warnings to the general public, intervene and regulate DS/N
Shortcomings:
- FDA receives inadequate scientifically based data regarding product safety
- FDA receives inadequate scientifically based data regarding product benefit
- FDA is unable to address the observed *potential* to do harm
- FDA is unable to verify manufacturing processes

FDA = Food and Drug Administration; DS/N = dietary supplements and neutraceuticals.

The DSHEA was designed with the goal of saving health care dollars by promoting self-healing as a vehicle to diminish costly doctor visits, drugs and diagnostic procedures. While there are obvious merits in patients assuming a primary responsibility for their own health, as exemplified by the USDA Dietary Guidelines for Americans (4), current data on the role of preventive medicine suggest that "self-healing" should not supplant physician visits and standards of care for screening, diagnostic testing and drug use. To illustrate the magnitude of this problem, expenditures for alternative medicine professional services increased 45% from 1990 to 1997, totaling $21 billion in 1997, $12 billion of which was paid for "out-of-pocket" expenses (5). An alarming 72% of patients availing themselves of alternative care failed to disclose this to their physicians (6). One can only

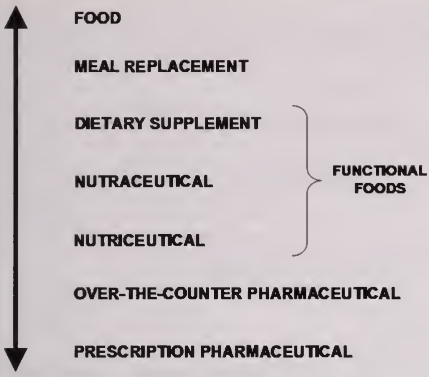

Figure. Spectrum of nutritional substances.

imagine the extent of this problem now, a decade later.

Moreover, as a result of DSHEA, there has been an explosion of commercially available DS/N, which has resulted in worrisome consequences. The FDA has recently succeeded in removing ephedra-containing products from the market. However, many other agents with reported adverse effects have not (yet) been banned. Until further legislation occurs that fairly reconciles the need of the general public to have access to safe DS/N, with their need to be protected from unsafe or inappropriate DS/N, physicians bear the responsibility to (a) educate themselves and their patients, (b) prescribe DS/N in a rational manner, (c) conduct research protocols to investigate the scientific merits of various DS/N, and (d) police the use of unproven therapies.

Another type of alternative care that has attracted traditional doctors is termed "functional medicine." This branch of alternative medicine focuses on the treatment of chronic diseases and symptoms, as well as preventive medicine and healthy aging. Though the use of traditional medicine is not prohibited, the use of DS/N is clearly favored. The rationale is predicated on physiologic theory, which can be quite intricate, as well as *in vitro* and preclinical studies, but without strong clinical data. However, there is a component of functional medicine that deserves mention. The use of genomic medicine in the realm of nutrition, so-called "nutrigenomics," represents an emerging field in traditional medicine that will one day, it is hoped, be commonplace. Specifically, gene arrays could be used to identify individualized nutritional needs to prevent diseases that would potentially occur later in life, such as type-2 diabetes mellitus, metabolic syndrome, cardiovascular disease, and various cancers, to name a few. The question is, "How appropriate would it be to start DS/N therapy for patients at risk for certain diseases?" The answer centers squarely on the presence and quality of clinical data to justify their use, and not simply theory, *in vitro* data, preclinical data, or imaginative aspirations.

"Evidence-based medicine" has become a frequent expression on hospital rounds and in heated debates on the relative merits of DS/N. Proponents of evidence-based medicine argue that all clinical decision-making must incorporate some level of scientific data to differentiate standard patient care from clinical investigations or purely impressionistic practices. Moreover, proper informed consent, risk-benefit analyses, and cost-effectiveness analyses can be based on the strength of the scientific evidence at hand and lead to formal recommendation grades (Table 2). Critics argue that one cannot extrapolate data from prospective, randomized controlled trials to a single patient, necessitating the incorporation of impressionistic, subjective attributes into any clinical decision. Besides, it is also asserted, even anecdote and testimonial constitute a form of "evidence."

Thus, the problem is: "When is it appropriate to prescribe or recommend DS/N?"

Navigating a Course towards the Answer

The rational use of DS/N has been approached via two converging methodologies. On the one hand, clinical investigators in traditional medicine have been reporting adverse events, case reports of apparent successes and relatively small prospective, randomized controlled trials for the use of DS/N for specific diseases. On the other hand, some alternative care practitioners have diligently conducted well-designed clinical studies to evaluate the safety and efficacy of many DS/N. The net result is an accrual of data that supports the use of some DS/N based on science and not hearsay (Table 3). Unfortunately, there are still many health care providers, both traditional and alternative, who recommend unproven (recommendation grade D) therapies, and practice quackery and profiteering. Patients who select these practitioners and substitute unproven therapies for standard medical care, must accept responsibility for their own choices and actions. Moreover—and this is a crucial point—even if a DS/N product is proven to be safe and effective with level I scientific evidence, there is no guarantee whatsoever that the commercially manufactured product actually contains: (a) the proper chemical structure of the main

TABLE 2
Levels of Scientific Substantiation

Level of Evidence	Recommendation Grade	Description
I		Well-controlled, generalizable, randomized trial Adequately powered Well-controlled multicenter trial Large meta-analyses with quality ratings All-or-none evidence
II		Randomized controlled trial—limited body of data Well-conducted prospective cohort study Well-conducted meta-analysis of cohort studies
III		Flawed randomized clinical trials Observational studies Case-series or case-reports Conflicting evidence with weight of evidence supporting the recommendation
IV		Expert consensus Expert opinion based on experience "Theory-driven conclusions" "Unproven claims"
	A	Homogeneous evidence from multiple, well-designed, randomized controlled trials with sufficient statistical power Homogeneous evidence from multiple, well-designed, cohort-controlled trials with sufficient statistical power ≥1 conclusive Level I publication demonstrating benefit >> risk **"first-line treatment"**
	B	Evidence from at least one large, well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis No conclusive Level I publication; ≥ 1 conclusive Level II publication demonstrating benefit >> risk **"second-line treatment"**
	C	Evidence based on clinical experience, descriptive studies, or expert consensus opinion No conclusive Level I or II publication; ≥ 1 conclusive Level III publication demonstrating benefit >> risk No conclusive risk at all and no conclusive benefit demonstrated by evidence **"no objection to use"**
	D	Not rated No conclusive Level I, II, or III publication demonstrating benefit >> risk Conclusive Level I, II, or III publication demonstrating risk >> benefit **"do not use"**

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ingredient; (b) the quantity of main ingredient indicated on the label; and/or (c) no other interfering substances or deleterious ingredients. Thus, the general, unregulated use of DS/N, particularly without the scrutiny of an individual's physician, confers more risk than benefit.

Clearly, additional scientific studies need to be conducted, so that eventually, level I meta-reviews can be generated to provide the basis for evidence-based recommendations for DS/N. In addition, a revamping of DSHEA, manufacturing processes of DS/N and the role of the FDA regarding DS/N are required.

TABLE 3
Summary of Results of Clinical Practice Guidelines for Some DS/N

DS/N	Indication	Recommendation Grade
Calcium	osteoporosis	A
Fiber	decreased risk of cancer and CAD	A
Folic acid	decreased risk of neural tube defects	A
Psyllium	decreased risk of CAD	A
Soy protein	decreased risk of CAD	A
n-3 fatty acids	cardiovascular disease	A
	hypertriglyceridemia	B
	inflammatory bowel disease	C
Chondroitin	osteoarthritis	B
Glucosamine	osteoarthritis	B
Probiotics	chronic pouchitis	B
	antibiotic-related diarrhea	C
Saw palmetto	benign prostatic hypertrophy	B
Ipriflavone	osteoporosis	B
Taurine	chronic alcoholism	B
	TPN-induced hepatopathy	C
α-lipoic acid	diabetic neuropathy	B
Coenzyme Q10	mitochondrial disorders	C
Creatine	performance enhancement	C
Androstenedione	performance enhancement	D
DHEAS	anti-aging	D
Melatonin	cancer	D
Ginkgo biloba	intermittent claudication	D

DS/N = dietary supplements and neutraceuticals; TPN = total parenteral nutrition; CAD = coronary artery disease; DHEAS = dehydroepiandrosterone sulfate.

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Summary of Recommendations

DS/N should be used in accordance with recommendations from clinical practice guidelines based on a technical review of the literature. Physicians should be aware that many DS/N have proven indications and that many others have no proven indications. Does this mean that DS/N must always have "strong" evidence demonstrating benefit in order to be rationally used? The answer is no. In some cases, the clinical evidence may demonstrate clear safety but unproven benefit (recommendation grade C). In this case, physicians should not actively recommend the use of the particular DS/N, but they need not instruct the patient to stop using it.

In situations where such clinical practice guidelines are not available, the individual practitioner should recommend DS/N only when a diligent literature search supports benefit exceeding risk and the patient has been fully apprised of these risks and benefits.

All patients should be asked about their use of DS/N, in addition to conventional medications, as part of routine history-taking.

Only DS/N manufactured properly should be used. Due diligence should be employed by the physician to verify that DS/N products meet this criterion. If a product cannot be verified, then the patient should be advised not to use it. Patients who choose to take unverified products would do so at their own risk.

Interactions between DS/N products—or between such products and food or medication—should be known by the physician. If there is any interaction that has potential for harm, the agent should not be recommended.

If a DS/N product is recommended, appropriate follow-up must be performed.

Physicians should receive formal education regarding DS/N in medical school, postgraduate training and continuing medical education programs. This will enable prudent and evidence-based decision-making, as well as facilitate communication with patients.

Research projects on DS/N with sound experimental design should be encouraged.

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Grand Rounds

Thrombotic Microangiopathy:

Differential Diagnosis, Pathophysiology and Therapeutic Strategies

Sebastian A. Mayer, M.D.[1], and Louis M. Aledort, M.D.[2]

Abstract

Several disease states manifest as thrombotic microangiopathies (TMA), most prominently thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The recent discovery of the von Willebrand factor cleaving protease ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif), found to be deficient in TTP, has helped separate these entities. In contrast, HUS is caused by direct endothelial damage by bacterial toxins, while in familial cases inappropriate complement activation through deficient factor H appears to be a major pathogenetic mechanism.

Although enormous progress has been made towards understanding these syndromes, the diagnostic tools and therapies used have hardly changed in the last 20 years, with the standard of care remaining plasma exchange in most cases. In this review, we will cover the multiple etiologic factors for TMAs, with the resultant differential diagnoses, as well as provide insight into the latest pathophysiologic findings and possible implications for treatment.

Key Words: Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, von Willebrand factor, ADAMTS 13, plasma exchange.

Introduction

First coined in 1952 (1), the term "thrombotic microangiopathy" (TMA) defines a pathologic alteration of the microvasculature, with detachment or swelling of the endothelium, amorphous material in the subendothelial space, and luminal platelet aggregation leading to compromise of the microcirculation (2).

There is a wide array of disease states that can present with a microangiopathic phenotype, the laboratory features of which almost uniformly include thrombocytopenia and hemolytic anemia with evidence of red blood cell fragmentation. The two most prominent diseases associated with thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). The former was first described by Eli Moschcowitz in 1925 as "an acute febrile pleomorphic anemia with hyaline thrombosis of the terminal arterioles and capillaries" (3) (in a case of a 16-year-old girl, who succumbed to her disease within 2 weeks). In 1955, Conrad Gasser gave the first account of the latter syndrome, reporting on 5 children with hemolytic anemia, thrombocytopenia and acute renal failure (4).

Decades after these first clinical observations, pathophysiologic insights have allowed us to differentiate these two phenomena on a molecular basis.

In this work, we will give an overview of the differential diagnosis, showing the variety of etiologies of microangiopathic anemia, review the latest findings in the pathophysiology of TTP and HUS, and discuss the current treatment options as well as some promising newer therapeutic approaches.

Epidemiology and Etiologic Factors in the Development of TMA

Idiopathic TTP is a rare disease, with about 500–2000 new cases diagnosed in the US each year; it exists in an acute form as well as a much

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[1] Fellow in Hematology/Oncology and [2] Professor of Clinical Research in Hemophilia, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Louis M. Aledort, M.D., Department of Hematology, Box 1006, Mount Sinai Medical Center, One East 100th Street, New York, NY 10029.

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rarer chronic relapsing variant. Women are affected about twice as often as men. HUS is slightly less common and shows a more balanced gender distribution, yet still has a female preponderance (5, 6). Apart from these idiopathic types, thrombotic microangiopathy has been associated with the use of a multitude of drugs, as well as with pregnancy, metastatic cancer, HIV and bone marrow transplantation (Table 1).

Drugs

As early as 1865, quinine was reported to cause purpura (7), and now both TTP and HUS are well-documented adverse effects of this drug. In a recent study, 14 of 132 patients with either TTP or HUS had been taking quinine, with the disease severity being the same as in idiopathic cases (8). Ticlopidine, an antiplatelet agent, was used as an adjunct in the treatment of TTP until it was discovered to cause the disease itself and was withdrawn from the market (9, 10). The similar agent, clopidogrel, has been associated with cases of TMA, albeit with a much lower risk (11).

Other groups of drugs documented in the development of TMA are the immunsuppressants cyclosporine and tacrolimus (12–15) as well as the cytotoxic cancer medications mitomycin C and gemcitabine (16, 17). Cisplatin and carboplatin have thus far been reported in a small number of cases of TMA (18–20).

Malignancy

Not only cytotoxic therapy but also the presence of cancer itself can cause TMA; tumors implicated are adenocarcinomas of the breast, gastrointestinal tract, prostate, and lung (21, 22).

HIV

HIV infection has been reported to portend a risk of developing TMA. The response of HIV-associated TMA treatment is similar to that of the idiopathic forms (23, 24). Current data suggest a role for direct endothelial damage by HIV (25).

TABLE 1
Etiologic Factors in Thrombotic Microangiopathy

Medications
Stem cell transplantation
HIV infection
Pregnancy
Autoimmune diseases
Malignancy
Shiga toxins
Idiopathic enzyme deficiency

Autoimmune Disorders

There have been occasional associations of TMA with systemic lupus erythematosus (SLE) (26, 27), ankylosing spondylitis (28), Sjögren's syndrome (29), polyarteritis nodosa (30), polymyositis (31), and Graves' disease (32). Given the paucity of the reports, however, one cannot draw firm conclusions about a causative context in these syndromes.

Bone Marrow Transplantation

In addition to the effect of cytotoxic drugs (16–20), the procedure of performing bone marrow transplantation has been identified as a cause for TMA, more frequently with allogeneic transplants than with autologous procedures. Procedure-related endothelial damage, in addition to medication effects, is thought to be an initiating factor (33, 34). Advanced age and female gender appear to be independent risk factors for post-transplant TTP (35).

Pregnancy-Associated TMA

The incidence of both TTP and HUS increases in pregnancy (36, 37), when they are often difficult to distinguish from hemolysis, elevated liver enzymes and low platelet count (HELLP), and severe pre-eclampsia (38).

Shiga Toxins

Shiga-toxin-producing *Escherichia coli* are the most common cause of HUS in children, although other bacteria have been reported (39, 40). In adults most cases of HUS are idiopathic; however, the pathogenesis of inherited HUS, as well as cases of sporadic HUS, have been tied to a deficiency in factor H (41, 42).

Idiopathic TTP

Some progress has been made in understanding idiopathic TTP, with the discovery of the von Willebrand Factor cleaving protease providing profound insights into the underlying pathology (43, 44).

Clinical Features and Differential Diagnosis

The classic pentad of TTP is defined as microangiopathic hemolytic anemia with schistocytosis (at least 3 cells per 100); severe thrombocytopenia (usually less than 10,000/mm^3); often fluctuating neurologic deficits secondary to central nervous system ischemia; fever; and renal abnormalities, including hematuria and/or proteinuria. However, only a minority of patients have fever, and renal involvement is not required for the diagnosis (6). Overt cerebral ischemia occurs in 50–75% of patients, making the presence of thrombocytopenia and schistocytes on the peripheral blood smear the sine qua non of the diagnosis (45, 46). A striking laboratory feature is a serum lactate dehydrogenase elevation that is often out of proportion to the degree of hemolysis, the source probably being hypoxic tissues in addition to lysed erythrocytes (47).

HUS, on the other hand, presents with similar, but milder blood count abnormalities, the main organ manifestation, however, being renal abnormalities, often severe enough to necessitate hemodialysis (48). The disease has been described in two variants. Diarrhea-associated HUS occurs predominantly in young children below the age of two years in epidemic outbreaks of *E. coli* O157:H7-related colitis (39). This form is usually self-limited, in contrast to idiopathic HUS, which commonly progresses to end-stage renal disease despite aggressive treatment (48).

Several similarly serious conditions can mimic TTP or HUS (Table 2), including disseminated intravascular coagulation (DIC) (49), the distinction of which is based on laboratory studies and the patient's history. Severe infections such as aspergillosis and cytomegalovirus have been reported to cause TMA as the result of vascular damage (50, 51). The need for antimicrobial treatment rather than plasma exchange dictates correct diagnosis of these disorders. Another fulminant illness that can be confused with TTP or HUS is the catastrophic antiphospholipid antibody syndrome (CAPS), in which widespread micro- and macrovascular thromboses with platelet consumption can occur. The detection of antiphospholipid antibody and prolonged activated partial thromboplastin time (aPTT) help distinguish CAPS from idiopathic TMA (52, 53).

TABLE 2

Conditions Which Mimic Thrombotic Microangiopathy

Disseminated intravascular coagulation (DIC)
Infections (aspergillosis, Rocky Mountain spotted fever)
Pregnancy-induced thrombocytopenias (pre-eclampsia, HELLP)
Vasculitis
Intravascular devices (prosthetic heart valves)
Malignant hypertension

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes and low platelet count

Among more common diseases, malignant hypertension can produce a clinical picture of TTP or HUS. However, the history of longstanding hypertension (a diastolic pressure above 130 mm Hg) and a retinal examination usually suffice to distinguish it (54, 55).

Although neither TTP nor HUS is specific to pregnancy, the incidence of both is increased in this setting (36, 37). These entities may be difficult to distinguish from other pregnancy-specific causes of microangiopathy, such as HELLP and severe pre-eclampsia (38). Usually, microangiopathic hemolysis is more severe in TTP and HUS than in the latter two disorders. Secondly, TTP develops relatively early in pregnancy, the mean onset time being after about 23 weeks, while pre-eclampsia and HELLP are usually encountered in the third trimester (56), and HUS occurs postpartum in 90% of the cases, with a median time to onset of 26 days (36). In contrast to cases of pre-eclampsia and HELLP, delivery does not ameliorate the course of pregnancy-associated TTP or HUS (37).

Systemic vasculitis has been reported to cause microangiopathic anemia, but in the vast majority of cases the dermatologic and orthopedic manifestations of this disease will guide one to the correct diagnosis (57).

Pathophysiology

Idiopathic TTP

The pathologic substrate of TTP is a thrombotic plaque in the microcirculation, composed mainly of aggregated platelets, with a small amount of fibrin (Table 3, 58). Although pivotal work by Brain has provided insight into the process of microangiopathic red cell fragmentation *in vivo* and *in vitro* by altered vascular surfaces and resultant rheologic disturbances (59, 60), the underlying biochemistry of the fulminant platelet aggregation remained unknown until the discovery of unusually large von Willebrand factor (vWF) multimers in TTP provided an important clue (61). A further milestone was reached with the discovery of defective degradation of vWF by a newly described metalloprotease (43, 44).

von Willebrand Factor

Mature vWF is composed of an aggregated subunit of 270 kD, assembled into multimers rang-

TABLE 3
Pathology and Mechanisms of Thrombotic Microangiopathies

Pathology	Mechanism	Disease
Systemic platelet thrombi	Inability to degrade large multimers of von Willebrand factor	Thrombotic thrombocytopenic purpura
Predominantly renal platelet-fibrin thrombi	Shiga toxins causing endothelial damage	Classic hemolytic uremic syndrome
	Factor H deficiency and complement activation	Familial hemolytic uremic syndrome
Systemic and renal thrombi	Drugs and stem cell transplantation with endothelial damage	Features of thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

ing from 500–10,000 kD. It is synthesized in megakaryocytes and endothelial cells, where it is stored in the Weibel Palade bodies (62). The multimers form filaments as long as 1300 nm (approximately the diameter of a platelet), and globular structures with a diameter of about 300 nm (63). vWF has functions in both platelet aggregation (64) and stabilization of factor VIII (65), and the size of the multimer directly correlates with its ability to support platelet aggregation by establishing strong bonds with the platelet glycoprotein Ib-IX-V complex (66).

Unusually Large vWF Multimers and Shear Stress

In 1982, Moake et al. found unusually large multimers of vWF (ULvWF) in the plasma of patients with chronic relapsing TTP (61). They demonstrated in serial measurements that, between episodes of active TTP, the ULvWF forms were present in the patients' plasma, whereas during an exacerbation of the disease they seemed to be cleared from the circulation, probably by consumption in the platelet thrombi. This observation led to the hypothesis of an inability of TTP-plasma to adequately degrade large vWF multimers (61).

Increased shear forces in the microcirculation have been shown to promote platelet aggregation, which can be mediated by platelet-derived vWF as well as by exogenous large vWF multimers. At high shear stress, platelets release vWF, which in concert with its exogenous counterpart binds to the exposed GPI-IX-V complex on the platelet, thus contributing to further apposition of a growing thrombotic lesion as the circulation becomes more compromised (67, 68). Shear-dependent platelet aggregation can be abrogated by inhibitors of vWF, lending further evidence to its crucial role in this setting (69). Globular vWF molecules on endothelial surfaces can be uncoiled under shear stress (70). This tensile stretching of ULvWF appears to be necessary for degradation by vWF-cleaving protease, suggesting their roles in forestalling uncontrolled platelet aggregation under shear stress (71).

VWF-Cleaving Protease (ADAMTS-13)

In 1996, Tsai and Furlan independently purified a plasma protease that cleaves vWF in a shear-dependent manner, creating the 140 kD and 176 kD fragments found in normal plasma (72, 73). Shortly thereafter, four patients, including two brothers, with chronic relapsing TTP were shown to have either substantially reduced or absent activity of the vWF-cleaving protease, without any inhibitors detected (74). This observation linked vWF-cleaving protease deficiency to the hereditary form of TTP, Upshaw-Shulman syndrome for the first time (75). The case of a patient with antibodies to vWF-cleaving protease and TTP suggested that acquired TTP might be an autoimmune disease (76). In the same year, two seminal studies showed that patients with TTP had severe deficiency of vWF-cleaving protease, whereas patients with HUS had normal levels. In most cases of non-familial TTP, an immunoglobulin G (IgG)-antibody to the protease was identified, supporting the notion of an autoimmune process. Of interest was the finding that patients with familial as well as non-familial HUS had normal protease levels, separating this entity from TTP on a pathogenetic level (43, 44).

The protease was identified as a member of the ADAMTS (a disintegrin and metalloprotease with thrombospondin type 1 motif) metalloprotease family (77). By means of genome-wide linkage analysis, the responsible gene was mapped to chromosome 9q34 (78). Thus far, more than 30 different mutations in the gene for ADAMTS-13 have been described in patients with the familial form of TTP, and none of these patients had an unmutated protease gene (79).

Although there are several conditions or situations with less pronounced reductions in ADAMTS-13 activity, namely DIC, idiopathic thrombocytopenic purpura (ITP), sepsis, SLE, heparin-induced thrombocytopenia (HIT), leukemia, cirrhosis, uremia, postoperative period, and the postnatal phase (80–83), evidence points towards a severe deficiency (less than 5%) of ADAMTS-13 to be specific for TTP (84). Difficulties in utilizing the protease activity as a diagnostic test remain, highlighted by a recent study finding that in a large series of clinically diagnosed TTP, the levels of ADAMTS-13 varied greatly between patients. Only 16 of 36 patients with idiopathic TTP and 2 of 10 with the pregnancy-associated form had severely depressed ADAMTS-13 activity (less than 5%). None of the other cases (stem cell transplant, drug-related, bloody diarrhea, HUS, HIV, and autoimmune diseases) were found to have such low enzyme levels. These results suggest that, at least for nonidiopathic TTP, alternative models of pathogenesis should be devised (85).

TTP Associated with Drugs and Stem Cell Transplantation

The mechanisms leading to drug-induced microangiopathy are poorly understood and most patients do not suffer from profound ADAMTS-13 deficiency (85). However, severe deficiency has been reported in cases related to ticlopidine (86) and clopidogrel (87). In both clinical settings, it was also possible to detect ADAMTS-13-inhibiting antibodies (86, 87). This contrasts with quinine-associated TTP, in which the formation of antibodies against platelets and endothelial cells was detected, suggesting a role for endothelial damage in promoting the thrombotic process (8).

Patients developing TTP after stem cell transplantation generally have normal ADAMTS-13 levels (88). Cyclosporine, widely used in the setting of allogeneic transplantation, can damage endothelial cells (89) and release tissue factor into the circulation (90). In concert with the graft-versus-host effect on the vascular integrity, cyclosporine is a major contributing factor to post-stem-cell-transplant TMA (88). To the contrary, in autologous transplantation, an autoimmune mechanism is believed to be at play, underlined by the positive response of the disease to cyclosporine, revealing the drug's dual effects (91). Apart from being a powerful immunosuppressant, however, cyclosporine can also increase nitric oxide production, which might also contribute to its beneficial effect in this particular setting (92).

Hemolytic Uremic Syndrome

Although the clinical distinction between TTP and HUS can be challenging, the differing histopathologies (93) and pathophysiologic pathways recommend HUS as a separate disease entity (94). In contrast to TTP, the pathologic lesion in HUS is a predominantly fibrin-containing thrombosis, largely confined to the renal circulation, yet present in other tissues in a fraction of cases (93).

The two thus far elucidated pathomechanisms leading to endothelial damage are toxin production by bacteria (40) and inappropriate activation of the complement system by deficient factor H (95).

Shiga Toxins and Endothelial Damage

Several strains of *E. coli*, most commonly O157:H7, produce shiga-like toxins, also known as verotoxins (for their lethal effect on Vero cells—African green monkey kidney cells), that are directly toxic to endothelial cells (96, 97). Once the toxin has entered the circulation it is bound to the surface of polymorphonuclear leukocytes (PMN) and transferred to glomerular endothelial cells, which have a 100-fold higher affinity for the toxin than for PMNs (98). The B subunit of the verotoxin binds to globotriaosyl ceramide (Gb3) on the endothelial cell membrane, leading to internalization of the A subunit. What follows is a breakdown of cellular protein synthesis from inactivation of the ribosome, and cell death in most cases (97). Sites of verotoxin-induced tissue damage coincide with areas of high Gb3 expression, especially the kidney (2). Once the stage has been set by endothelial damage, upregulation of cytokine production, PMN activation and enhanced oxidant injury potentiate the damage done, leading to a weakening of antithrombotic mechanisms (99). In addition to fibrin deposition, the appearance of ULvWF multimers contributes to local platelet aggregation (100), and the ensuing narrowing of the arteriolar lumen leads to renal dysfunction (101).

Defective Factor H and HUS

Factor H is a regulatory protein that inhibits complement activation via the alternative pathway by preventing the formation of the C3bBb complex and accelerating the dissociation of Bb from C3 convertase. By modulating complement activation, factor H plays an important role in attenuating the inflammatory response to local vascular insults (102). For HUS, activation of both the classical and alternative complement pathways has been well documented, with resolution if the disease remits (103). In cases of familial HUS, C3 levels were consistently depressed independently of the disease activity, and normal levels of C4 ruled out activation of the classic pathway (104). So far, studying families with cases of familial HUS has provided insight into several function-altering mutations of factor H associated with HUS, demonstrating autosomal dominant as well as recessive inheritance (42, 105–107). Since only 2–7% of patients exposed to verotoxin-producing *E. coli* progress to overt HUS, a genetic predisposition has long been suspected. Recent descriptions of polymorphisms in the promotor and coding regions for factor H have been described. There is speculation as to whether these might give rise to heightened susceptibility to environmental factors (94).

Therapy and Prognosis

For decades TTP was an almost uniformly lethal disease, until plasma infusion therapy was shown to have some clinical benefit (108), but the real breakthrough came with the introduction of plasma exchange, with long-term remission rates of 80–90% (45, 46). A randomized trial clearly demonstrated superiority of plasma exchange versus infusion, both in remission induction and long-term follow-up (45). It is believed that, while plasma transfusion provides the absent or defective vWF-cleaving protease, concomitant plasmapheresis removes autoantibodies against ADAMTS-13, ULvWF multimers and other potentially detrimental factors from the circulation. Supporting this notion, exchange has successfully been employed with cryosupernatant, which does not contain larger vWF polymers, in patients not responding to regular plasma exchange (109). Recurrent episodes in chronic relapsing TTP can successfully be treated with plasma- or cryosupernatant only, in retrospect understood due to the deficiency of ADAMTS-13 in the absence of an inhibitor (110–112). It is generally agreed that once the diagnosis of TTP is suspected, plasma exchange should be started as soon as possible. If delays are unavoidable, the therapy can be started with fresh frozen plasma infusions until definitive therapy can be arranged. The duration of therapy is variable, since responses can take up to one month to become manifest and the exchange needs to be continued for about one week in excess of a complete remission, in order to avoid early relapse. Since fragmented red cells may not be cleared from the circulation for a few days, the platelet count and serum LDH are the most reliable laboratory parameters to assess treatment success. It is prudent to include steroids, since it was shown that prednisone can by itself induce remission in TTP, albeit at a very low rate (108).

Since not all TMA is TTP, it is not surprising that the response to exchange therapy is not universal, as seen in the case of stem-cell-transplantation-related TMA, which carries a mortality of 80%, and for which the effect of plasma exchange could not be distinguished from that of cyclosporine discontinuation (113, 114).

Recent data suggest that ADAMTS-13 level at diagnosis predicts the response to exchange and survival. In a prospective analysis, patients with idiopathic TTP and ADAMTS-13 levels below 5% had a mortality of 15%, in stark contrast to patients with stem cell transplantation-, cancer-, drug- or pregnancy-related TMA, whose mortality was as high as 59%. Of note, none of these patients had ADAMTS-13 levels below 5% (115). Plasma exchange is also indicated in non-shiga-toxin-associated HUS, the efficacy being lower than for TTP, with relapse rates between 29 and 82% (45, 46, 116).

Childhood *E. coli*-associated HUS does not warrant plasma therapy, since it usually resolves spontaneously (116). Nevertheless, it is not a benign disease, with a mortality of 3–5% and a similar proportion of patients developing end-stage renal disease (117).

Although there are some anecdotal reports on beneficial effects of intravenous immunoglobulin (IVIG) on TMA, a controlled study with 44 patients could not confirm any improvement from adding IVIG to plasma exchange (118–120).

The role of splenectomy was never studied in a controlled fashion, but the experience reported thus far supports its role in relapsed TTP and refractory cases (121–123). Protein A immunoabsorption, designed to remove IgG from the circulation, has produced remissions in patients resistant to plasma exchange, but no comparative studies exist (124). Other immune-modulating approaches have employed cyclophosphamide- and azathioprine-containing regimens; however, the low number of successfully treated cases prohibits any firm conclusions (125, 126).

Another cytostatic drug, vincristine, has been applied not for its immunotoxic effect, but to exploit its microtubule-destabilizing property for platelet stunning (127).

Emerging Treatments

The humanized monoclonal antibody to CD20, rituximab, holds promise in cases of resistant TTP, by decreasing antibody production (128, 129). A prospective trial is underway to evaluate its role in TTP. Although there is still controversy as to whether severe ADAMTS-13 deficiency is specific for TTP (130, 131), it will be interesting to evaluate the role of recombinant ADAMTS-13 (132) as treatment at least for hereditary TTP. Such studies should help lead to more disease-specific therapy and reduction of the high burden of toxicity and infection risk associated with the current standard of care.

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Grand Rounds

Recent Diagnostic and Therapeutic Innovations in Heart Failure Management

ANIL K. GEHI, M.D., SEAN P. PINNEY, M.D., AND ALAN GASS, M.D.

Abstract

Although there has been substantial progress in the treatment of congestive heart failure over the last several decades, it is clear that heart failure continues to burden our aging population. As the epidemic of heart failure grows, there remains an unmistakable need for novel diagnostic and therapeutic options in its management. In this article, we review recent innovations in the management of congestive heart failure, highlighting several recent clinical trials.

Key Words: Heart failure, diagnosis, therapy, innovations, review.

Introduction

ACCORDING TO THE NATIONAL HEART, Lung and Blood Institute (NHLBI), approximately 5 million people in the United States have been diagnosed as having congestive heart failure (CHF) (1). Each year approximately 550,000 people are diagnosed with CHF, with the incidence approaching 1% after age 65. For those diagnosed with CHF, the annual mortality is approximately 45%, and 80% will die within 5 years, a prognosis worse than that of the majority of cancers (2).

Hospital admissions for CHF account for $3.6 billion in Medicare expenditures for 990,000 admissions each year (2). The total annual cost to the health care system approaches $25 billion. And 20% of all hospital admissions are for CHF. Among persons older than 65, the rate of CHF hospitalization increased by 159% in the last decade (1). The number of hospitalizations of patients with a principal diagnosis of CHF has increased steadily over the past 2 decades and is expected to double during the next 40 years as the result of the progressive aging of the Western population (3). Given this growing epidemic, considerable effort continues to be made to reduce the number of hospitalizations, decrease the morbidity and mortality, and improve the quality of life of those suffering from heart failure.

Current Therapies

In the past two decades, there has been substantial progress in the treatment of heart failure. A multitude of clinical trials have demonstrated the benefits of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta-blockers, aldosterone antagonists, biventricular pacing, and the use of multidisciplinary teams to treat failure (1, 4, 5). These interventions have clearly been shown to reduce morbidity and mortality, reduce the rate of hospitalizations, and improve the overall functional status of patients with systolic congestive heart failure.

However, it is important to realize the limitations of these advances. Despite the results of clinical trials, large epidemiologic surveys fail to show any meaningful change in overall death rates. Rather, death from CHF seems only to have been delayed after the initial diagnosis (1). Furthermore, the actual prescribing of medications with proven benefit in systolic congestive heart failure contin-

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The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Anil Gehi, M.D., Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: anil.gehi@msnyuhealth.org

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ues to be woefully inadequate. A recent survey of more than 33,000 outpatient visits for CHF showed that ACE inhibitors are still used by only 39% of patients (6) and beta-blockers by only 30–40% of eligible patients (7). Before considering novel approaches, we must first make considerable effort to remedy this deficiency.

Many new and exciting diagnostic and therapeutic innovations have recently been developed. This review will highlight the hypotheses and important evidence for many of these innovations.

Diagnostic Innovations

B-Type Natriuretic Peptide

An important recent advance in evaluating the patient with congestive heart failure is the use of B-type natriuretic peptide. To provide rapid and effective treatment for patients with heart failure, accurate differentiation of heart failure from other causes of dyspnea must be established. In chronic heat failure, a reliance on physical signs to assess ventricular filling pressures may be misleading (8). An objective, easily available assessment of the severity of heart failure may help direct aggressive therapy for those patients with the worst prognoses.

B-type natriuretic peptide (BNP) is a neurohormone released from the cardiac ventricles in response to increased wall tension (9). The “BNP” (Breathing Not Properly) study evaluated BNP levels using a rapid, bedside assay of 1,586 patients who presented to the emergency department with acute dyspnea. When compared with the clinical diagnosis of congestive heart failure by two independent, blinded cardiologists, the diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83.4%. The negative predictive value at levels less than 50 pg/mL was 96% (9).

In a second study, 250 predominantly male patients presented with dyspnea at an academic Veteran’s Affairs hospital. At a blood concentration of 80 pg/mL, BNP was an accurate predictor of the presence of CHF (95%) when compared with a consensus of two cardiologists. A concentration less than 80 pg/mL had an excellent negative predictive value (98%) (10).

In a prospective study of 1,050 patients with or without CHF, BNP levels increased with CHF severity as determined by New York Heart Association (NYHA) class, but were only statistically significant when comparing individuals with and without CHF, using a cutoff of 100 pg/ml (11). Individuals without CHF had a median BNP of 9.29 pg/mL. Median BNPs among patients with NYHA classes I–IV were 83.1, 235, 459, and 1,119 pg/mL, respectively.

In a randomized study of 69 patients with CHF, therapy was guided by BNP or standard clinical assessment. At 6 months’ follow-up, BNP-guided therapy reduced total cardiovascular events and delayed time to a first event, compared with clinically guided therapy (12).

Additionally, BNP levels have been found to correlate with the risk of death, heart failure, and myocardial infarction (MI) in patients presenting with acute coronary syndrome (ACS). A baseline level of BNP at presentation with an ACS correlates with outcomes at 30 days and 10 months in a stepwise fashion, in increasing quartiles of BNP levels (13). BNP levels may also enable risk stratification to predict sudden cardiac death in patients with heart failure. In a study of 452 patients with heart failure and an EF < 35%, using a cutoff of 130 pg/mL, sudden-death-free survival was significantly higher in patients below (99%) compared with patients above (81%) this cutoff (14).

In summary, the BNP assay has clearly been shown to be beneficial in ruling out heart failure as a cause of dyspnea when an upper limit of 80–100 pg/mL is used. At values greater than 300 pg/mL, the BNP assay points to cardiac disease as a contributing factor to dyspnea, although the BNP assay does not distinguish between different etiologies of heart failure. However, an elevated BNP level, regardless of etiology, portends a worsened prognosis for a number of outcomes, including risk of death, heart failure, MI, and sudden cardiac death. The utility of the BNP assay for an individual patient, as a means of following the progression of heart failure and response to treatment has not yet been established, but is presently being evaluated.

C-Reactive Protein

As the inflammatory model of atherosclerotic disease has emerged, C-reactive protein (CRP) has been studied as a marker of systemic inflammation. In the last several years, an elevated CRP has been shown to be an independent predictor of the development of atherosclerosis, and prognostic of future cardiovascular events (15).

In this context, recent studies have found an elevated CRP to be a predictor of the development of both heart failure and heart failure admission. CRP levels were measured in a cohort of 732 elderly Framingham Study subjects free of prior MI or heart failure. After a mean follow-up of 5.2 years, a serum CRP level ≥ 5 mg/dL was found to be associated with a 2.8-fold increased risk of CHF (16). In the ABC (Health, Aging, and Body Composition) study, incident coronary heart disease, stroke and CHF events as well as blood levels of IL-6, CRP, and tumor necrosis factor (TNF)-alpha were assessed during a mean follow-up of 3.6 years among 2,225 elderly patients without baseline cardiovascular disease. CRP was found to be significantly associated with CHF events (17).

In a prospective study of 76 patients with heart failure admitted to the hospital, CRP levels, NYHA class, and ejection fraction (EF) were assessed. CRP levels were found to trend higher in relation to EF and NYHA class at discharge. At 18 months of follow-up, patients with CRP levels > 0.9 mg/dL were more likely to be readmitted for heart failure. In multivariate analysis, CRP level remained predictive of readmission, independent of NYHA class and EF (18).

Therapeutic Innovations

Neurohormonal Agents

As the neurohormonal model of heart failure has become more accepted, several new neurohormonal agents have emerged as potential therapies in heart failure. These agents antagonize the neurohormonal reflexes that have detrimental effects on the heart or augment the reflexes that may be beneficial in maintaining organ perfusion.

Nesiritide

Therapeutic options for patients hospitalized with acute exacerbations of chronic heart failure are limited. Inotropes such as dobutamine and milrinone achieve short-term hemodynamic improvement and symptomatic relief; however, they consistently fail to show improvements in mortality or length of hospital stay (19). Nesiritide is a recombinant human BNP, an important counter-regulatory neurohormone in the pathogenesis of heart failure, recently approved for the treatment of patients hospitalized with decompensated heart failure (20).

In an initial efficacy trial of 127 patients, intravenous nesiritide had beneficial hemodynamic effects on patients with decompensated CHF, decreasing pulmonary capillary wedge pressure (PCWP) by 9.6 mm Hg at 6 hours (21). Other hemodynamic trials have shown nesiritide to be effective in also reducing mean right atrial pressure and systemic vascular resistance, while being accompanied by a significant increase in cardiac index, without a significant effect on heart rate (20). Additionally, nesiritide has been found to have a vasodilatory effect on coronary arteries, augmenting coronary artery blood flow (22).

The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial was a multicenter, randomized, double-blind trial of 489 inpatients with dyspnea and decompensated CHF. It randomized intravenous nesiritide to nitroglycerin in addition to standard medications for 24 hours. At 3 hours and 24 hours, there was an increased reduction in PCWP in the nesiritide group compared with the nitroglycerin group, but no significant difference in dyspnea (23).

The PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) trial randomized 255 patients with decompensated CHF to nesiritide or dobutamine. At 24 hours, dobutamine significantly increased the number of ventricular tachycardia (VT) events, PVCs, and heart rate (HR) compared with nesiritide, while both drugs were similarly effective in improving the signs and symptoms of CHF (24).

Recently, the FUSION-1 (Follow-Up Serial Infusions of Natrecor) trial demonstrated that three months of weekly infusions of nesiritide could be safely administered to recently hospitalized outpatients. Subset analyses suggested reduced mortality or hospitalization for selected high-risk patients (25). The larger, multicenter FUSION-2 trial will investigate whether the benefit of weekly nesiritide infusions persists once the infusions are stopped.

To date, however, there are no long-term data showing decrease in length of hospitalization, readmission rate, or mortality, with nesiritide.

Omapatrilat

Atrial and brain (B-type) natriuretic peptides (ANP and BNP) as well as adrenomedulin and bradykinin are metabolized by neutral endopeptidase (NEP). NEP inhibitors increase plasma concentrations of these counter-regulatory neurohormones. Omapatrilat, an orally active, long-acting inhibitor of NEP and ACE, is the most prominent of a class of agents known as vasopeptidase inhibitors. Initial efficacy trials, including a randomized, double-blind hemodynamic study of 369 patients with symptomatic heart failure treated with omapatrilat, demonstrated an acute reduction in PCWP, systolic blood pressure, and systemic vascular resistance that was maintained after 12 weeks (26).

The IMPRESS (Inhibition of Metaloprotease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure) trial of 573 patients with NYHA Class II–IV heart failure randomly assigned patients to omapatrilat, an inhibitor of neutral endopeptidase and ACE or lisinopril. After 24 weeks, there was a trend towards benefit in the combined endpoint of death and admission for worsening heart failure (27). Omapatrilat improved heart failure class among those patients with more severe (NYHA III–IV) symptoms when compared with lisinopril (27).

The larger OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial was powered for morbidity and mortality endpoints to assess long-term efficacy in heart failure. In this randomized trial of 5,770 patients with NYHA Class II–IV heart failure, which compared enalapril to omapatrilat, there was no difference in the primary combined endpoints of all-cause mortality and heart failure hospitalizations (28). Furthermore, the 2.17% incidence of angioedema found in the OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) trial, studying the efficacy of omapatrilat in hypertension, has led to further concerns about this novel agent (29).

Vasopressin Receptor Antagonists

Arginine vasopressin (AVP) is a powerful vasoconstrictor and antidiuretic agent present at increased levels in heart failure. In addition to having deleterious effects on body fluid regulation and hemodynamics, accumulating evidence suggests that AVP can cause structural changes in the myocardium (30). AVP acts via V1 receptors found on the blood vessel and in the myocardium as well as V2 receptors found on the renal tubule.

A double-blinded trial of 143 patients with symptomatic NYHA Class III or IV heart failure randomized patients to short-term treatment with intravenous conivaptan, a dual V1a/V2 AVP receptor antagonist or placebo. At 6 hours after infusion, those on conivaptan had increased urine output and a significantly reduced PCWP and right atrial (RA) pressure compared with placebo, although there were no significant changes in cardiac index, systemic or pulmonary vascular resistance, blood pressure, or heart rate (31).

A trial of 254 patients with heart failure randomly assigned patients to oral tolvaptan, a selective V2 AVP receptor antagonist, or placebo. After 25 days, the patients randomized to tolvaptan had reduced body weight, edema, and normalized serum sodium, with no significant change in heart rate, blood pressure, renal function, or quality of life (32).

Results from the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure) trial were recently reported (33). The study randomized 319 patients hospitalized with heart failure to tolvaptan or placebo within 72 hours of admission, for up to 60 days. The patients taking tolvaptan had a major reduction in body weight and a normalization of serum sodium within 24 hours, which was sustained at discharge. There were no differences between the groups in coronary heart failure at 60 days.

A long-term clinical efficacy study in progress known as EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure), similar in design to ACTIV, will enroll 3,600 patients. This trial is expected to be completed in 2005.

Thromboxane Inhibitors

The decline in renal plasma flow in heart failure leads to the renal production of such vasoconstrictor neurohormones as prostaglandin F2 (PGF2) and thromboxane A2 (TxA2) to preserve glomerular filtration. Persistently increased TxA2 levels such as exist in heart failure can worsen renal function (34).

Picotamide, an oral renal TxA2 / PGH2 receptor inhibitor was administered in a study of 14 patients with NYHA Class IV heart failure in an 8-day, randomized, double-blind cross-over study. Compared with placebo, effective renal plasma flow and glomerular filtration rate increased. After 8 days of treatment, picotamide was associated with an increase in diuresis, an improvement in serum creatinine, a decrease in pulmonary artery and right atrial pressure, a decrease in body weight, and a corresponding reduction in dyspnea (34).

Endothelin Antagonists

Endothelin is a potent vasoconstrictor with remodeling effects similar to those of angiotensin II. Plasma endothelin levels are elevated in patients with heart failure and increase with worsened hemodynamics and symptoms (35). Several selective and non-selective endothelin receptor antagonists are under investigation, although for the most part results have been discouraging.

Bosentan is an oral, non-selective endothelin receptor antagonist, currently approved for use in patients with pulmonary hypertension; it has not yet shown efficacy in heart failure. Though early trials were encouraging, the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trial, which randomized 1,613 patients with NYHA Class III–IV heart failure to bosentan or placebo, failed to show benefit in morbidity or mortality at 1-year follow-up (36).

Darusentan, an oral, selective endothelin A receptor antagonist, was studied in the EARTH (Endothelin Antagonist Receptor Trial in Heart Failure) trial (37). This trial, which randomized 642 patients to darusentan or placebo, found no benefit in clinical or physiological outcomes.

Tezosentan is an encouraging intravenous dual endothelin A/B receptor antagonist. In an efficacy, dose-finding trial, 292 patients admitted to the hospital with an exacerbation of heart failure were randomized to tezosentan or placebo. After 6 hours of therapy, patients treated with tezosentan had decreased PCWP and increased cardiac index compared with those on placebo (38–40).

Other Neurohormonal Agents

Several other neurohormonal agents undergoing investigation have as yet failed to show efficacy in heart failure. Moxonidine is a centrally acting sympathetic outflow inhibitor with encouraging hemodynamic actions. Early trials involving patients with Class II–III heart failure demonstrated neurohormonal benefit (41). However, the larger MOXCON (Sustained Release Moxonidine for Congestive Heart Failure) mortality trial was stopped prematurely due to an excess of adverse events (42). Nolomirole, an inhibitor of dopaminergic and adrenergic outflow, which has shown promise in animal studies (43), is currently undergoing further investigation in the ECHOS (Echo Cardiography and Heart Outcome Study) trial.

Statins

Even though statins are of proven benefit to patients with ischemic heart disease, their potential use by patients with non-ischemic heart failure has been suggested, given their anti-inflammatory and vascular protective effects (44). In a study of 63 patients with symptomatic, non-ischemic, dilated cardiomyopathy, patients were randomized to receive simvastatin 10 mg/day or placebo. After 14 weeks, those on simvastatin, while demonstrating only a modest reduction in serum cholesterol, had a significantly lower NYHA functional class and an improved EF when compared with those taking placebo. This benefit corresponded to lower concentrations of TNF-alpha, IL-6, and BNP (44). Two large prospective trials of rosuvastatin use in heart failure (GISSI-HF and CORONA) will attempt to resolve this matter.

Immunomodulators

Congestive heart failure is associated with elevated levels of TNF-alpha. Several experimental studies have suggested involvement of TNF-alpha in the pathogenesis of heart failure (45).

In a small trial, 47 patients with NYHA Class III or IV heart failure were randomized to etanercept, a TNF-alpha inhibitor, or placebo. After 3 months of therapy, patients on etanercept showed an improvement in LV function and a trend towards improvement in functional status (46). However, in the RENEWAL trial, a combination of the RENAISSANCE (Randomized Etanercept North American Strategy to Study Antagonism of Cytokines) trial and the RECOVER (Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction) trial, which randomized a total of 1,800 patients to etanercept or placebo—there was no benefit in the combined endpoints of death and CHF hospitalization after 12 months' follow-up (47). In the ATTACH (TNF Therapy against Congestive Heart Failure) trial, a study which randomized 150 patients with NYHA Class III or IV heart failure to infliximab (another TNF-alpha inhibitor) or placebo, there was actually an increase in the combined endpoints of death and hospitalization for heart failure at 28 weeks' follow-up (48). However, the effects of TNF-alpha inhibition in patients with NYHA Class I or II are unknown.

Another form of immune modulation therapy recently reported supports the role of immune activation in the pathogenesis of heart failure. Weekly injections of autologous blood exposed to oxidative stress, which previously were shown experimentally to reduce inflammatory cytokines and increase anti-inflammatory cytokines, were studied in a phase II trial (49). Among 75 patients randomized to immunomodulatory therapy, at six months' follow-up, there was a significantly reduced risk of death and hospitalization and a trend towards improved quality of life. A phase III trial of this encouraging therapy, known as ACCLAIM (Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy), is currently underway.

Matrix Metalloproteinases

The cardiac extracellular matrix is composed of an extensive network of collagens. Collagen cross-linking is an important factor in the systolic and diastolic function of the heart. In response to myocyte damage, hemodynamic load, or neurohormonal factors, the extracellular matrix of the heart undergoes remodeling. This remodeling is controlled by the interplay of matrix metalloproteinases (MMPs) that degrade collagens and inhibitors of metalloproteinases (TIMPs). Various cytokines (such as TNF-alpha and IL-6) and neurohormones (such as norepinephrine, angiotensin

II, and endothelin) upregulate MMP expression. Several animal studies have suggested that modulation of MMPs and TIMPs may be an exciting new direction in the prevention and treatment of heart failure, although there remain many concerns of potential adverse consequences of therapy (50, 51)

Anticoagulation

The relative risk of stroke associated with heart failure varies from as much is 4.1 among those aged 50–59 to 1.5 by age 80–89, reflecting the greater proportion of strokes resulting from other causes (52). Retrospective analyses of the SAVE (Survival and Ventricular Enlargement) and the SOLVD (Studies of Left Ventricular Dysfunction) trials have shown that the rate of stroke is inversely proportional to EF. Furthermore, retrospective analyses of the SOLVD data demonstrated a highly significant reduction in mortality for those patients with ischemic or non-ischemic left ventricular dysfunction treated with warfarin (52). Several large prospective randomized trials have sought to answer this question.

The WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial of patients with heart failure and an EF ≤ 35 was designed to enroll 4,500 patients with 5-year follow-up and a primary outcome of death, stroke, or myocardial infarction. WATCH was to include a third treatment arm randomizing patients to clopidogrel (52). Recently reported at the 2004 American College of Cardiology Scientific Sessions, WATCH was halted prematurely due to a lack of patient enrollment. With only 1,587 patients, there was no difference in death, MI, and stroke between aspirin and warfarin at 23 months' follow-up.

The WASH (Warfarin / Aspirin Study in Heart Failure) trial, also limited by poor patient enrollment, randomized 279 patients to no antithrombotic therapy, aspirin, or warfarin. Again no difference was found in clinical outcomes at 27 months (53).

The WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial is an ongoing study randomizing patients with heart failure and an EF ≤ 30% to warfarin (target INR 2.5–3.0) or aspirin. The trial of 2,860 patients will accumulate 5-year follow-up data with the primary outcome being all-cause mortality and stroke. Perhaps when outcomes of this trial are combined with those of WATCH and WASH, a clearer answer to the question of antithrombotic therapy will be available. However, with available data, long-term warfarin therapy cannot be recommended.

Anemia

Approximately half of all patients with heart failure are anemic (hemoglobin < 12g%) (54). The prevalence and severity of this anemia appear to increase with increasing severity of CHF. In a study of 142 patients at an outpatient CHF clinic, the mean Hb concentration decreased from 13.7% in mild CHF (NYHA class I) to 10.9% in severe CHF (NYHA class IV). There was an associated increase in the prevalence of Hb < 12% from 9.1% of patients in NYHA class I to 79.1% in NYHA class IV (55). This anemia is believed to be caused by a number of factors, including poor nutrition, associated renal insufficiency causing inappropriately low erythropoietin levels, bone marrow depression, erythropoietin resistance caused by excessive TNF-alpha, gastrointestinal blood loss from various antiplatelets and anticoagulants, and hemodilution caused by the excessive plasma volume (54). An analysis of the SOLVD trial showed that the level of hematocrit (Hct) was an independent risk factor for mortality. During a mean follow-up of 33 months, the mortality was 22%, 27%, and 34% for those with a Hct > 40%, 35–40%, and < 35%, respectively (56).

A randomized controlled trial of 32 patients with moderate-to-severe CHF (NYHA III–IV), whose Hb levels were persistently between 10.0 and 11.5%, addressed the question of whether treating the anemia improved outcomes. Silverberg et al. treated patients with subcutaneous erythropoietin (EPO) and IV iron to increase the level of Hb to at least 12.5%. After an average follow-up of 8.2 months, the mean NYHA class improved (42.1% vs. 11.4%), the left ventricular ejection fraction increased (+5.5% vs. –5.4%), the need for furosemide decreased, and the number of days spent in the hospital decreased, for those patients treated with EPO and IV iron (57). Additionally, in a randomized trial of 26 anemic patients with CHF, Mancini et al. found that those randomized to EPO had significant improvement in exercise capacity after a follow-up of 3 months (58).

Sinus Rhythm

The prevalence of atrial fibrillation increases as the severity of heart failure increases, ranging from 4% in those with minimally symptomatic CHF (NYHA Class I–II) to approximately 50% in those with severe symptoms (NYHA Class IV) (59). Patients with atrial fibrillation have a worse prognosis than those without it. In the SOLVD-Prevention trial, atrial fibrillation was independently associated with an increased all-cause mortality at 3 years, from 23% to 34%. The DIG trial similarly demonstrated a relative risk (RR) of mortality of 2.45 and RR of hospitalization of 3.0 at a mean follow-up of 38 months for those in atrial fibrillation (59).

The onset of atrial fibrillation may be associated with a decrease in cardiac output and a worsening of heart failure that is multifactorial. Loss of atrioventricular synchrony can result in impaired diastolic filling, reduced stroke volume and an approximately 20% reduction in cardiac output. An irregular ventricular response elevates right atrial and pulmonary capillary wedge pressure, worsening many of the symptoms of CHF. Cellular and extracellular remodeling occurs as a result of atrial fibrillation. Patients with atrial fibrillation have higher levels of atrial natriuretic peptide and endothelin. Tachycardia in patients with a rapid ventricular response can lead to a reduction in ventricular function (59).

Subset analyses of two randomized trials have demonstrated improved survival among patients with heart failure and atrial fibrillation who reverted to sinus rhythm. The CHF-STAT trial randomized 674 patients with ischemic and non-ischemic NYHA Class III–IV heart failure to amiodarone or placebo. Among those patients who at baseline were in atrial fibrillation, those who converted to sinus rhythm on amiodarone, compared to those who did not, were found to have a significantly lower mortality (60, 61). The DIAMOND (The Danish Investigators of Arrhythmia and Mortality on Dofetilide Study Group) trial randomized 1,518 patients with CHF and atrial fibrillation to dofetilide or placebo. At one-year follow-up, 61% of patients treated with dofetilide vs. 33% on placebo had reverted to sinus rhythm. While overall mortality in the dofetilide group was not significantly different from that of the placebo group, for those patients with restoration of sinus rhythm, there was a significant reduction in mortality (RR=0.44) (62).

Even though these trials did not show an overall improvement in outcomes with antiarrhythmic therapy, there appeared to be a benefit in patients who converted to sinus rhythm. As newer, more effective techniques for the maintenance of sinus rhythm emerge, this issue should be readdressed.

Non-pharmacologic Options: Exercise

Until the early 1980s, it was thought that significant left ventricular systolic dysfunction was a contraindication to exercise (63). However, following early reports of enhanced exercise capacity and enhanced ventricular reserve with exercise training, a number of small trials demonstrated physiologic benefits from exercise training, including increased peak oxygen consumption, increased peak cardiac output, reduction in sympathetic nervous system activity, improved endothelial function, and decreased insulin resistance (63).

More recently, larger randomized trials have called attention to the importance of exercise training. A 1999 study of exercise training in heart failure randomized 110 patients with stable CHF to an exercise regimen of exercise training 2–3 times per week or no exercise. At one-year follow-up, exercise training was associated with improved quality of life, decreased mortality (RR=0.37), and decreased hospital readmission for heart failure (RR=0.29) (64). The ELVD-CHF (Exercise in Left Ventricular Dysfunction and Chronic Heart Failure) trial, reported in 2003, randomized 90 patients with stable chronic heart failure to a 6-month exercise training program or no exercise. At 6 months, LV volumes diminished and EF improved for the exercise group, with a corresponding improvement in walking distance and quality of life. There was also a trend towards fewer hospital admissions for patients randomized to exercise (65).

Given the available evidence supporting exercise training for patients with heart failure, the Committee on Exercise, Rehabilitation, and Prevention of the American Heart Association Council on Clinical Cardiology has concluded that exercise training is safe and beneficial in improving exercise capacity and quality of life. The committee advocates exercise training programs for patients with chronic heart failure (66).

Conclusion

As the epidemic of heart failure continues to grow, medical science continues to make enormous gains in the management of the disease. Our understanding of the mechanism of disease progression has led to a shift in drug development from that of enhancing cardiac function to that of inhibiting the detrimental effects of the neurohormonal axis. As this review demonstrates, considerable effort in the development of novel therapies is underway. Very soon our options for treatment will expand greatly. We can only hope that these novel approaches continue to extend survival and enhance quality of life among those suffering from heart failure.

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Preoperative Cardiovascular Evaluation for Noncardiac Surgery

THOMAS M. MADDOX, M.D.

Abstract

Cardiovascular complications following noncardiac surgery constitute an enormous burden of perioperative morbidity and mortality. Annually, more than one million operations are complicated by adverse cardiovascular events, such as perioperative myocardial infarction or death from cardiac causes. In order to combat this problem, cardiac evaluation prior to noncardiac surgery should ask two questions about the patient: What is the risk of cardiac complications during and after surgery? How can that risk be reduced or eliminated?

Risk assessment evaluates patients' co-morbidities and exercise tolerance, as well as the type of surgery to be performed, to determine the overall risk of perioperative cardiac complications. Previous or current cardiac disease, diabetes and renal insufficiency all confer higher risks for perioperative cardiac complications. Poor exercise tolerance and high-risk surgical procedures (e.g., vascular, prolonged thoracic or abdominal operations) also predict worse perioperative outcomes. Noninvasive stress testing is widely used to help predict risk of perioperative complications, but the poor predictive power of these tests hampers their usefulness.

After estimating the risk of cardiac complications, one should take measures to reduce it. Beta blockade has shown clear benefits in risk reduction. At this time, there are no data suggesting benefits of percutaneous coronary intervention or coronary artery bypass grafting in reducing noncardiac surgical risk. In addition, angioplasty with stenting and its attendant need for anticoagulation can expose patients to increased risk of perioperative bleeding. Thus, the use of coronary revascularization prior to noncardiac surgery should be reserved for those patients with an independent cardiac need for the procedure, such as unstable angina or stable angina refractory to medical therapy.

In summary, patients with low clinical risk factors and good functional status, undergoing a low or intermediate risk surgery, have an excellent prognosis and may proceed to surgery without further delay. In addition, stable patients who have previously undergone coronary revascularization may also safely undergo surgery. Patients requiring urgent surgery should proceed immediately, since the consequences of delay usually outweigh the benefits of preoperative risk assessment. However, elective surgery should be indefinitely deferred for those patients with unstable coronary syndromes, since consequences of the cardiac disease usually negate the benefits of surgery. Controversy involves the intermediate or high clinical risk patient considering high-risk, but elective, surgery. Noninvasive testing offers only limited assistance in estimating risk for these patients. The best risk reduction strategy for these patients is perioperative beta blockade use. The role of coronary revascularization specifically to reduce perioperative cardiac complications remains unproven.

Key Words: Coronary artery disease, perioperative care, percutaneous coronary intervention, coronary artery bypass grafting, intra-operative complications, postoperative complications, risk assessment, risk factors, surgical procedures.

CARDIOVASCULAR COMPLICATIONS following noncardiac surgery constitute an enormous burden of perioperative morbidity and mortality. Approximately 30 million patients have surgery annually in the United States and almost one-third of them have coronary artery disease (CAD) or risk factors for its development. More than one million operations are complicated by adverse cardiovascular events, such as perioperative myocardial infarction (MI) or death from cardiac causes (1). In high-risk populations, such as patients undergoing vascular surgery, the incidence of perioperative MI can reach 34% (2, 3). Perioperative MI causes substantial morbidity and prolonged hospitalizations, and has mortality rates as high as 25–40% (2, 3). The economic effects of these complications are also sobering, with annual costs estimated at $20 billion (4).

Given these numbers, it is hardly surprising that surgeons and anesthesiologists frequently consult cardiologists to "clear" a patient for noncardiac surgery. Cardiac evaluation prior to noncardiac surgery should ask two questions about the patient: What is the risk of cardiac complications

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Address all correspondence to Thomas M. Maddox, M.D., Zena and Michael A. Wiener Cardiovascular Institute, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029-6574; email: tmaddox@alumni.rice.edu

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during and after surgery? How can that risk be reduced or eliminated? While the questions may be straightforward, the answers are far from clear.

Cardiac Risk Assessment

Ideal risk evaluation has several components. It should be accurate, meaning the clinical criteria used to evaluate patients are significant predictors of adverse cardiac outcomes. Risk evaluation should also be efficient, so that each clinical variable collected adds independent and useful information to the overall risk assessment. Finally, it should be timely, providing information quickly, so as not to cause unnecessary delays in the decision to perform or postpone the planned surgery. These considerations are also important in the use of provocative tests of cardiac function. Such testing should accurately stratify patients into lower- and higher-risk groups, add independent information to the overall risk assessment, and avoid unnecessary delays or added risks in the process (1).

Risk evaluation is only the first step in preoperative evaluation. Once this risk is quantified, clinicians must then be able to act on the information. Are there interventions to significantly reduce risk? Do these interventions expose the patient to potential harm or cause unnecessary delays in surgery? Does the benefit of the intervention justify the risks? The availability of effective interventions also has implications for clinical risk assessment; if there is no therapy to attenuate cardiac risk, then the value of obtaining additional testing is questionable. With careful consideration of these principles, preoperative risk assessment and reduction can serve as powerful tools to enable clinicians to optimize patients' cardiac health during the perioperative period.

The most recent American College of Cardiology (ACC)/American Heart Association (AHA) practice guidelines recommend assessment of patients' co-morbidities and exercise tolerance, as well as the type of surgery to be performed, to determine the overall risk of perioperative cardiac complications (5). Based on this assessment, selected patients should undergo provocative cardiac testing; others may require interventions to mitigate risk.

Clinical Risk Indices

Over the past 25 years, several models for assessing perioperative cardiac risk have been described. In 1977, Goldman et al. described a cardiac risk index for patients undergoing general, orthopedic, or urologic surgeries. Evidence of cardiac ischemia or failure, arrhythmias, older age, valvular disease, poor medical condition, or need for high-risk surgery identified patients at high risk for perioperative cardiac complications (6). Nine years later, Detsky et al. described a risk index with enhanced predictive power for patients undergoing vascular or general surgeries (7).

Most recently, Lee et al. offered a cardiac risk index that provided an effective yet simple method of assessing risk (2). The authors studied 4,315 patients, aged 50 years or older, who had undergone elective major noncardiac surgeries. Approximately half of the patients were assigned to a derivation cohort to establish predictive clinical variables, while the other half were assigned to a validation cohort to test the index. Six independent predictors of cardiac complications were identified: high-risk surgery (procedures with a 5% or higher risk of cardiac complications, such as vascular and prolonged intraperitoneal or intrathoracic operations); history of ischemic heart disease; history of congestive heart failure; history of cerebrovascular disease; preoperative treatment with insulin; and preoperative serum creatinine > 2.0 mg/dL.

When patients were stratified by these criteria, rates of major cardiac complications with 0, 1, 2, or 3+ criteria were 0.5%, 1.3%, 4%, and 9%, respectively, in the derivation cohort. There was no significant difference in complication rate between those with 0 or 1 clinical factor, but meaningful differences in complications occurred between these groups and the two higher-risk groups. When the model was applied to the validation cohort, the model's predictive power remained. In another assessment of its power, the index was compared to the Goldman and Detsky risk indices using Receiver Operating Curves (ROC). The Lee index had significantly greater predictive power than the other two indices.

Despite its predictive power, Lee's model is not without flaws. It is underpowered to investigate the relationship between risk class and cardiac complications for patients undergoing abdominal aortic surgery. Since the study was conducted with patients at a single teaching hospital, the ability to generalize its findings is somewhat limited. The index was also designed to be simple, using only dichotomous variables to assess risk. Thus, some accuracy may have been sacrificed in the pursuit of simplicity—perhaps a reasonable tradeoff in pursuit of a practical prediction tool. Despite these limitations, the Lee index remains a valuable tool for predicting risk. Based on this and related studies, the ACC/AHA guidelines currently classify patients at intermediate clinical risk for complications if they suffer from a previous MI, angina, heart failure, diabetes, or renal insufficiency (5).

Functional Capacity Assessment

The guidelines also recommend that a patient's functional capacity be incorporated into the overall risk assessment (5). This recommendation comes from a study of 600 outpatients undergoing noncardiac surgery (8). Patients were classified with good or poor exercise tolerance based on their self-reported ability to either walk 4 blocks or climb 2 flights of stairs. Significant differences in the clinical characteristics of these two groups were noted; the poor-exercise-tolerance group had higher numbers of patients with congestive heart failure, hypertension, and diabetes. Not surprisingly, calculation of the Detsky cardiac risk index for these patients (the Lee index had not been published at the time of this study) illustrated higher risk scores in the poor exercise tolerance group (7). During the perioperative period, the rates of major adverse cardiac events (i.e., cardiac death and MI) were similar for the two groups. However, minor complications, such as myocardial ischemia and neurological events, occurred with greater frequency in the poor exercise tolerance group. Accordingly, exercise capacity assessment has a role in preoperative risk calculation.

Surgical Risk

The nature of the planned surgical procedure is an important factor in risk assessment. Vascular surgeries are especially prone to cardiac complications, with rates exceeding 5%, presumably due to the high concurrence of CAD and peripheral vascular disease (PVD), the masking of CAD symptoms secondary to the exercise impairment associated with PVD, as well as the length of operation and substantial fluid shifts inherent in such surgeries (10). Additionally, several large surveys have demonstrated that perioperative cardiac mortality is elevated among patients who undergo major thoracic, abdominal, or vascular surgery, especially when they are 70 years old or older (11 – 15).

Noninvasive Diagnostic Testing

As with clinical risk assessment, noninvasive diagnostic testing must be used judiciously. Effective testing should be accurate, add useful information to the overall risk assessment, and avoid unnecessary delays in surgery. In addition, testing should be performed only when it will lead to therapies that are proven to reduce perioperative cardiac risk (1).

Myocardial perfusion imaging. Stress myocardial perfusion imaging is widely used to assess perioperative risk. By virtue of vasodilator use, perfusion imaging can be used for nearly all patients, even those whose medical conditions preclude exercise (e.g., PVD). A positive test result occurs when heterogeneity in radionuclide activity is demonstrated in different segments of the myocardium. Whether this finding can reliably predict cardiac risk is unclear. In reports of patients undergoing vascular surgery, the percentage of patients with positive perfusion tests ranged from 23 – 69%, but the positive predictive value of the test for perioperative cardiac complications was only 4 – 20% (5). The negative predictive value, in contrast, remained uniformly high at approximately 99% (5). Thus, though a negative perfusion test result can offer substantial reassurance to patients and physicians alike, the predictive power of a positive test is poor.

In addition, even when perfusion imaging provides an accurate prediction of increased risk, it may not add independent prognostic value beyond that of clinical risk stratification. Vanzetto et al. illustrated effective stratification of high-risk patients undergoing abdominal aortic surgery using perfusion imaging. Patients with a normal scan had a cardiac event rate of 2%, while those with thallium redistribution had a rate of 23% (16). Another study, by Bartels et al., closely paralleled the ACC/AHA guidelines in its assessment of patients, allowing both high- and intermediate-risk patients with a low functional capacity to receive thallium imaging. Abnormal results prompted further cardiac management (not specified), and the subsequent rate of perioperative cardiac complications did not differ significantly across risk groups (17). Though these results offer support for the use of perfusion imaging, the lack of a control group and the heterogeneity of cardiac management of those patients with abnormal scans weaken these conclusions.

Importantly, a large, blinded, prospective study by Baron et al. revealed that myocardial perfusion imaging did not provide independent prognostic value beyond that of clinical risk stratification. Definitive clinical evidence of CAD and age over 65 years old were better predictors of cardiac complications (18).

Dobutamine stress echocardiography. Dobutamine stress echocardiography (DSE) is another test widely used to predict perioperative risk. DSE evaluates left ventricular regional wall motion at rest and during dobutamine stress. The test's adrenergic stimulation offers a better approximation of the stress encountered during the perioperative period than that provided by vasodilators (1). Unfortunately, the accuracy of the test in predicting cardiac complications is similar to that of perfusion imaging. The data indicate that the range of positive test results for patients undergoing vascular surgery is 9 – 50%, with a positive predictive value for cardiac complications ranging from 7 – 25%. The negative predictive value ranges from 93 – 100% (5). However, DSE does appear to add incremental information to risk assessment in certain selected cases. A study by Boersma et al. illustrated that stress-induced ischemia on DSE independently predicted perioperative cardiac complications in high-risk patients undergoing vascular surgery. Furthermore, those with more extensive ischemia (> 4 wall segments involved) carried a higher risk of complications than did those with more limited ischemia (19). The recent ACC/AHA guidelines corroborate this finding, stating that the weight of the evidence supports the use of DSE for assessing preoperative risk for properly selected patients, especially those undergoing peripheral arterial revascularization (5).

In summary, the appropriate use of noninvasive testing in the assessment of perioperative cardiac complications is controversial. The low positive predictive value of both myocardial perfusion imaging and DSE greatly hampers their accuracy. Whether or not additional information regarding cardiac risk can be derived from these tests is also unclear, although the evidence seems to imply a greater role for DSE than for myocardial perfusion in stratifying high-risk patients. The greatest concern, however, lies with the next step. Once the risk of cardiac complications is estimated, what interventions can mitigate it?

Therapy to Reduce Perioperative Risk

Medical Therapy

Several medical treatments have been proposed to help reduce cardiac risk in noncardiac surgeries. The most extensively studied treatment is beta blockade. Mangano et al. studied the effects of atenolol administered to high-risk patients two days prior to their noncardiac surgeries (20). There was no difference between the atenolol and control groups in perioperative cardiac complications, but a long-term mortality benefit in the atenolol group was demonstrated at 6 months. Poldermans et al. studied the perioperative use of bisprolol in elective major vascular surgery (3). Patients with at least one clinical risk factor and demonstrable ischemia by dobutamine stress echo were given bisprolol an average of 37 days prior to their surgeries and to achieve a resting heart rate at or below 60 beats per minute (bpm). Notably, patients with extensive wall motion abnormalities on echo, arguably the highest-risk patients, were excluded from the study. Nonetheless, perioperative MI and death from cardiac causes were reduced by 91% in the bisprolol group.

Using the same cohort of patients from the Poldermans study, Boersma examined the effect of bisprolol, as stratified by clinical risk score and DSE results. In patients with fewer than 3 clinical risk factors (low or intermediate risk in the revised cardiac risk index), bisprolol significantly reduced cardiac complications compared to controls. Similarly, patients with 3 or more clinical risk factors and a DSE with wall motion abnormalities in 4 or fewer segments also demonstrated a significant decrease in cardiac complications with the use of bisprolol. However, high clinical risk patients with wall motion abnormalities in 5 or more segments did not benefit from perioperative use of bisprolol (19). Taken together, these two studies illustrated that bisprolol, started well before noncardiac surgery, can substantially reduce perioperative cardiac complications in all but the highest-risk patients. Questions remain as to whether these findings extend to all types of beta blockers, as well as the optimal initiation time of therapy. In addition, patients with severe left ventricular dysfunction were excluded from these studies, so the role of perioperative beta blockade in this population is unknown (1). Nonetheless, the convincing findings of Poldermans and Boersma confirm a salutary role for beta blockade in a substantial number of cardiac patients.

Other medical therapies under investigation include alpha-2 receptor agonists, nitrates, calcium channel blockers, and statins. Patients with established CAD undergoing vascular surgery were treated perioperatively with the alpha-2 agonist mivazerol. Compared to controls, there was a significant reduction in MI and death from cardiac causes (21). However, these results were not duplicated in another placebo-controlled, randomized, blinded study of mivazerol (22). In that study, no differences in perioperative death or MI were observed between treatment and control groups, although significantly less myocardial ischemia occurred in the mivazerol group. Studies with clonidine did not illustrate a reduction in death and MI, although a lower incidence of intraoperative myocardial ischemia was noted (23). Nitrate use to reduce intraoperative ischemia has had uneven effects, with no apparent reduction in incidence of MI or cardiac death (24, 25). Studies of calcium channel blockers have been too small to draw meaningful conclusions on their use (26). Finally, Poldermans et al. studied the use of statin therapy in patients undergoing major vascular surgery at a single medical center (27). The statin group had a significant reduction in perioperative mortality compared to the placebo group. More recently, an observational study by Lindenauer et al. supported these findings by illustrating a reduction in death perioperatively for patients receiving statins (28). Despite these initial promising studies, beta blockade is the only medical therapy with conclusive evidence of cardiac risk reduction at the current time.

Coronary Artery Bypass Grafting

No randomized, controlled trials show benefit of coronary artery bypass grafting (CABG) surgery in attenuating the risks of noncardiac surgery (4). However, several observational studies have examined the incidence of perioperative cardiac complications among noncardiac surgical patients who had previously undergone CABG surgery for coronary artery disease. Fleisher et al. found that CABG revascularization in anticipation of aortic surgery was not associated with improved perioperative survival, but that it benefited long-term mortality (29). Eagle et al. examined CABG patients from the Coronary Artery Surgical Study (CASS) database who had undergone subsequent high-risk noncardiac surgeries. Compared to patients without previous CABG, the revascularized patients experienced significantly fewer cardiac complications perioperatively (30). More recently, an analysis of the Bypass Angioplasty Revascularization Investigation (BARI) trial found that patients revascularized, either by CABG or percutaneous coronary intervention (PCI) had similarly low rates of postoperative cardiac complications. Taken together, these retrospective studies imply a low risk of cardiac complications for patients who have recently undergone CABG surgery. Accordingly, the ACC/AHA guidelines recommend that asymptomatic patients who have undergone CABG in the previous five years should proceed directly to noncardiac surgery without further preoperative evaluation (5).

Despite these findings, CABG is not recommended for asymptomatic patients *solely* for the purpose of reducing the risks of noncardiac surgery. The risk of CABG surgery, combined with the delay in needed noncardiac surgery, usually outweighs the potential risks of proceeding with surgery. Two studies, one by Mason et al. and the other by Fleisher et al., validated this concept. Both demonstrated that performing CABG prior to vascular surgeries can be harmful—chiefly by exposing the patients to multiple surgeries and their risks (31, 32). Thus, CABG surgery should be performed, and noncardiac surgery delayed, *only* if there are independent indications for CABG surgery.

Percutaneous Coronary Intervention

In many centers, findings of ischemia or CAD during noninvasive testing lead to coronary catheterization and potentially to PCI (usually balloon angioplasty with stenting) of associated plaques. Although a trial assessing the role of PCI and CABG in reducing surgical risk is currently underway, currently no data suggest benefit of PCI in reducing noncardiac surgical risk (5, 33). Several cohort studies have illustrated a low incidence of cardiac complications in PCI patients during noncardiac surgery, but none of those studies had control groups (34–36). Interestingly, Posner et al. showed no benefit of PCI in preventing perioperative cardiac complications when performed within 90 days of surgery (37). More recently, Landesberg et al. investigated the role of revascularization in reducing cardiac risk (38). The study compared two groups of patients with high clinical risk and moderate-to-severe reversible thallium perfusion scans undergoing major vascular surgery. One group received coronary revascularization, while the other proceeded directly to surgery. The revascularization group had significant long-term survival at 5 years. However, the study failed to report the incidence of perioperative MIs, and there was no significant mortality benefit noted at either 30 days or 1 year. In light of these limited findings, the use of PCI prior to noncardiac surgery should be reserved for those patients with an independent need for the procedure (i.e., those with unstable angina or stable angina refractory to medical therapy).

In summary, the risk of cardiac events during noncardiac surgery can be mitigated, but only with beta blockade. As investigation continues, there may be roles for other drug therapies, as well as for coronary revascularization. However, as new methods of risk reduction emerge, each must be evaluated in the context of its benefits, risks and delays to the planned surgery.

Noncardiac Surgery Safety and Coronary Stenting

The recent use of coronary stenting in the treatment of CAD introduces a new wrinkle in preoperative evaluation. Placement of coronary stents causes complete denudation of the arterial endothelial surface, greatly increasing the risk of thrombosis (39, 40). Fortunately, this risk is attenuated with the use of combined antiplatelet therapy (aspirin and clopidogrel) and improvements in stent deployment. Currently, the incidence of stent thrombosis is less than 1% (41).

The impact of noncardiac surgery on stent thrombosis, and thus the optimal delay of the surgery after coronary stenting, is unknown. Surgery promotes, and by necessity requires, thrombosis (41). Surgical stress activates the sympathetic nervous system, which may indirectly trigger adverse cardiac and vascular outcomes. Plasma procoagulant clotting factors increase and fibrinolysis decreases, resulting in a hypercoagulable state and potentially increasing the thrombosis risk to recently placed stents (42). In addition, the use of antiplatelet agents in the perioperative period is problematic. Their essential role in preventing stent thrombosis may simultaneously increase the risk of surgical bleeding to unacceptable levels.

Initial studies investigating noncardiac surgery soon after coronary stenting are instructive. Kaluza et al. followed 40 patients who underwent noncardiac surgery (mostly vascular) within 6 weeks of receiving a coronary stent and noted 7 MIs, 11 major bleeding episodes, and 8 deaths (43). All of the deaths and MIs, as well as most of the bleeding incidents, occurred within 2 weeks of stent placement. Predictably, most of the adverse events resulted from either in-stent thrombosis or uncontrolled bleeding due to the use of antiplatelet drugs. A larger study by Wilson et al. examined 207 patients undergoing noncardiac surgery within two months of receiving coronary stenting (41). All adverse events (MI and death from cardiac causes) occurred within 6 weeks of stent placement, although the overall rate of complications was much lower than that in the Kaluza study. No events occurred in patients undergoing surgery 7–9 weeks after stent placement. Based on these and related studies (44, 45), current ACC/AHA recommendations suggest delaying noncardiac surgery for a minimum of 4, and preferably 6 weeks (5).

Future innovations in PCI will require ongoing evaluation. The use of coronary brachytherapy appears to prolong the re-endothelialization of coronary arteries, which may necessitate longer waiting periods after stenting, before surgery can be performed safely (46). Similar concerns surround drug-eluting stent use, and these require investigation. The role of heparin-coated stents also needs definition. Some interventionalists advocate their use to avoid the need for oral antiplatelet therapy and its concomitant bleeding risks during surgery. Although some early trials have suggested low rates of thrombosis with these stents, no randomized controlled trials have evaluated their role in stent thrombosis prevention, either in general or in preparation for noncardiac surgery (9, 47). Further research is required before their use can be recommended.

In summary, coronary stenting in CAD treatment has significant implications for noncardiac surgery timing. At this time, guidelines recommend 6 or more weeks of recovery and antiplatelet use after PCI before undergoing surgery. The risks of surgical delay must be weighed against the benefits of PCI.

Conclusions and Recommendations

Successful perioperative evaluation and management of high-risk cardiac patients undergoing noncardiac surgery requires careful teamwork and communication among the surgeon, anesthesiologist, primary care physician, and cardiology consultant (5). In general, patients with low clinical risk factors and good functional status, undergoing a low- or intermediate-risk surgery, have an excellent prognosis and may proceed to surgery without further delay. In addition, stable patients who have recently undergone coronary revascularization may also safely undergo surgery, provided sufficient time for recovery from the revascularization procedure has elapsed. At the other end of the spectrum, patients requiring urgent surgery should proceed immediately, regardless of cardiac risk, since the consequences of delay usually outweigh the benefits of perioperative cardiac risk assessment. However, elective surgery should be deferred indefinitely for those patients with unstable coronary syndromes, since consequences of the cardiac disease usually negate the benefits of surgery.

The most controversial area of perioperative evaluation, then, lies with the intermediate or high clinical risk patient considering high-risk, but elective, surgery. Noninvasive testing appears to offer limited assistance in stratifying the risks of these patients, with the best evidence pointing to dobutamine stress echocardiography as the test of choice. Once risk is identified, the most effective intervention is the use of beta blockade. The role of coronary revascularization specifically to reduce perioperative cardiac complications remains uncertain.

Efforts to define more clearly the role of noninvasive imaging and PCI in cardiac risk estimation and reduction are needed. In addition, with improvements in our ability to diagnose and treat CAD and ischemia, incorporation of this new knowledge into risk assessment will be important.

Finally, in an era when the best practices entail not only the highest quality care for the individual but also the best use of societal resources, determination of the most cost-effective strategies to evaluate and prevent perioperative cardiac complications is crucial.

As the population continues to age, conducting effective cardiac risk assessment will become increasingly important. Knowing what to do and, equally important, what not to do, will be central to this task.

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HIV-Associated Nephropathy:

A Brief Review

Ting-chi Lu, M.D., and Michael Ross, M.D.

Abstract

HIV-associated nephropathy (HIVAN) is an important cause of renal failure in HIV-1 seropositive patients. The disease is characterized by collapsing focal segmental glomerulosclerosis with marked podocyte proliferation, microcystic dilatation of the tubules and interstitial nephritis. Patients generally present with advanced HIV-1 infection, renal insufficiency and marked proteinuria. No serologic markers exist to diagnose HIVAN, and given the broad differential diagnosis for renal failure in these patients, renal biopsy should be performed. Viral infection of renal cells plays a central role in the pathogenesis of HIVAN. There is now compelling evidence that highly active antiretroviral therapy (HAART) is effective in preventing end-stage renal disease in patients affected with HIVAN. The efficacy of angiotensin-converting enzyme (ACE) inhibitors and prednisone has also been evaluated, but larger prospective studies are needed.

Key Words: Nephropathy, glomerulosclerosis, nephritis.

Introduction

HIV-ASSOCIATED NEPHROPATHY (HIVAN) is a renal syndrome in HIV-1 seropositive patients, characterized by heavy proteinuria, renal dysfunction and rapid progression to renal failure. It was initially described in 1984 by Rao et al., who reported a pattern of sclerosing glomerulopathy in HIV-1 seropositive patients in New York City (1). It is now the third leading cause of end-stage renal disease (ESRD) in African Americans between the ages of 20 and 64 and the most common cause of ESRD in HIV-1 seropositive patients (2).

Patient Population

HIVAN is usually a late manifestation of HIV-1 infection; however, it has been reported to be the initial presentation of HIV-1 infection (3). Winston et al. evaluated 10 patients with biopsy-proven HIVAN. Although 50% of the patients were asymptomatic and had not suffered from opportunistic infections at the time of diagnosis, all had CD4 cell counts of less than 200 cells/mm^3. Furthermore, after reviewing prior studies of HIVAN in which CD4 cell counts were available, the authors found that of a total of 114 patients reported, only 6 did not have a CD4 cell count below 200 cells/mm^3 (480 – 1700 cells/mm^3) (4).

HIVAN is especially prevalent among patients of African descent (1, 5, 6). In the US, blacks are 12.2 times more likely to develop HIVAN than non-black patients (7). In the largest reported series from Europe, 97 of 102 patients with HIVAN were black (8).

Clinical Presentation

Patients typically present with renal insufficiency accompanied by proteinuria that is usually in the nephrotic range (9). In a study of 26 patients with HIV-1 associated nephropathy, the mean 24-hour protein excretion rate was 6.6 grams per day, with a mean serum creatinine concentration of 5.4 mg/dL (10). Despite the presence of heavy pro-

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Department of Nephrology, Mount Sinai Medical Center, New York, NY.

Address all correspondence to Ting-chi Lu, M.D., Mount Sinai Hospital, Department of Nephrology, Box 1243, One East 100th Street, New York, NY 10029.

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teinuria, peripheral edema is uncommon. Hypertension is also surprisingly rare in most patients with HIVAN, leading some to speculate that HIVAN is a salt-wasting disease (8).

There are no specific serologic or urinary markers for HIVAN. Co-infection with hepatitis B and C is common and should be considered in all patients suspected to have HIVAN, because they are associated with membranous nephropathy and membranoproliferative glomerulonephritis, respectively. Renal ultrasound generally shows echogenic kidneys that are normal-to-large in size (11, 12).

In the evaluation of an HIV-1 positive patient, the first step is to rule out acute and reversible causes of renal failure. The differential diagnosis of renal failure is similar to that in non-HIV-1-infected patients. Complications of their underlying illness such as poor oral intake, chronic diarrhea and vomiting may predispose patients to prerenal azotemia and acute tubular necrosis. Furthermore, HIV-1 patients are frequently exposed to medications that can adversely affect renal function. For example, acute tubular necrosis can be caused by pentamidine, foscarnet, cidofovir, amphotericin B or aminoglycosides. Renal calculi and tubulointerstitial crystal deposition can be caused by indinavir. Many antibiotics such as trimethoprim sulfamethoxazole are capable of inducing interstitial nephritis (13).

Even after most acute causes of renal failure are ruled out, only approximately 50% of suspected cases are confirmed to be HIVAN after renal biopsy. Common alternate findings are mesangioproliferative glomerulonephritis and IgA nephropathy. Studies that have reported biopsies of patients with potential HIVAN have found a wide range of renal diseases such as amyloidosis, minimal change disease, diabetic nephropathy, allergic interstitial nephritis, and cryoglobulinemia, instead of HIVAN (4, 14–16). Therefore, for patients suspected of having HIVAN, it is important for a kidney biopsy to be performed, to establish the diagnosis.

Clinical Course and Prognosis

In the absence of treatment with highly active antiretroviral therapy (HAART) or angiotensin-converting enzyme (ACE) inhibitors, most patients with HIVAN progress to end-stage renal disease within weeks to months from the time of diagnosis (11). Mortality is generally a result of other AIDS-related complications. In an early study, Carbone et al. showed that the survival rates of HIVAN patients were similar to those of patients with AIDS (11). Mortality in patients with ESRD due to HIVAN is high (approaching 50% in one study) but is improving with the widespread use of HAART (8).

Epidemiology

In the United States, the current prevalence of HIVAN is probably underestimated, since the US Renal Data System (USRDS) only accounts for cases that have progressed to end-stage renal disease (1; Fig. 1). With the advent of HAART and ACE inhibitors, there are many cases of HIVAN now that do not progress to ESRD as rapidly as they did in the past. In order to determine the true prevalence, one study evaluated 557 HIV-1 seropositive patients using urinalysis. Those with > 1.5 g/day of proteinuria were biopsied. In this study, the incidence of HIVAN in African-American patients with HIV-1 was 3.5%; no cases were identified in non-black patients (16). A recent study reviewing autopsies of HIV-1 seropositive patients found that among black patients, 12% had HIVAN at the time of death. The higher prevalence of HIVAN in this series may be due to advanced AIDS in many of these patients (17).

With the continued increase of HIV-1 infection around the world, HIVAN is likely to become an increasingly prominent problem. In 2003 alone, more than 3 million people in sub-Saharan Africa were estimated to have been infected with the virus. Worldwide, only 7% of people who need anti-retroviral therapy have the means of obtaining it (18). This could translate into a large number of patients with end-stage renal disease due to HIVAN.

Pathology

Light microscopy of HIVAN biopsies is characterized by frequently collapsing focal glomerulosclerosis. The term “collapse” refers to an implosive retraction of the glomerular basement membrane. There is marked hypertrophy and hyperplasia of the overlying visceral epithelial cells. These cells may display mitotic figures and intracytoplasmic protein resorption droplets (14, 19; see Fig. 2a). Other histological findings include microcystic dilatation of the tubules. Microcysts are tubules that have at least three times the outer diameter of normal tubules. This is accompanied by atrophy and flattening of the tubular epithelial cells (20). Prominent lymphocytic infiltration of the interstitium is frequently present (see Fig. 2b). Electron microscopy may show numerous tubuloreticular structures in glomerular endothelial cells (14). On immunofluorescence, there may be staining for IgM, C3 and less frequently, C1 (9).

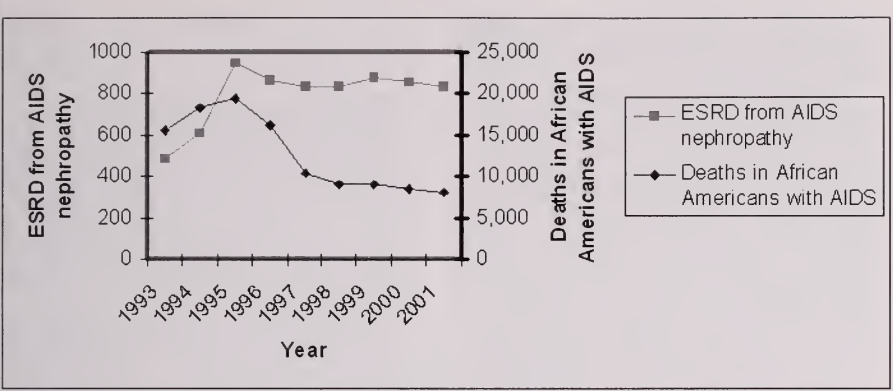

Fig. 1. Trends in ESRD due to HIV-associated nephropathy and mortality in African Americans with AIDS. U.S. Renal Data System, USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government (2).

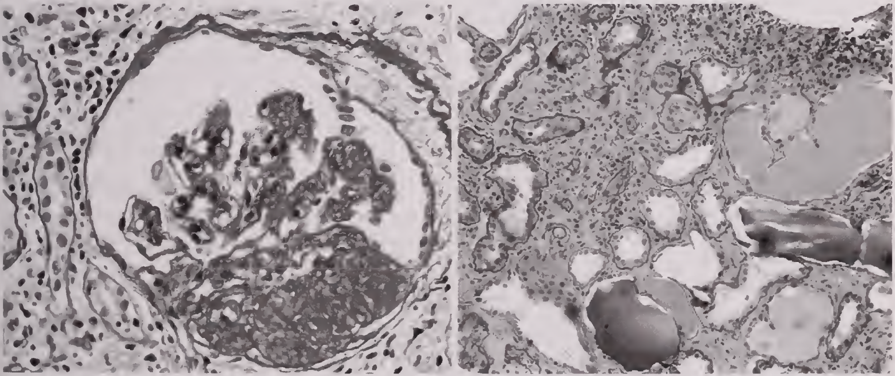

Fig. 2. Light microscopy from human biopsy with HIVAN. **A.** Characteristic collapsing focal segmental glomerulosclerosis with podocyte proliferation. **B.** Microcystic tubular dilatation and inflammatory interstitial infiltrates.

Pathogenesis

Animal studies have greatly added to our understanding of HIVAN pathogenesis. An HIV-1 transgenic mouse expressing a gag/pol deleted, replication-defective proviral construct develops renal disease very similar to HIVAN in humans, with proteinuria and progressive azotemia (21, 22). Studies using animal models of HIVAN suggest that the renal pathogenesis is due to viral infection of the renal cells rather than immune dysregulation in the setting of systemic HIV-1 infection. One study used reciprocal kidney transplantation between wild-type and HIV-1 transgenic mice to demonstrate the importance of viral gene expression in causing HIVAN. The HIV-1 transgenic mice that received transplants from nontransgenic littermates did not develop kidney disease, whereas normal non-transgenic mice that received transplants from HIV-1 transgenic mice did develop HIVAN. This suggests that renal transgene expression is a necessary component in the development of kidney disease (23).

In humans, the presence of HIV-1 in renal epithelial cells has been shown. One study examined human kidney biopsy samples from HIV-I seropositive patients. Using *in situ* hybridization, HIV-I RNA was detected in renal epithelial cells. The presence of HIV-I was further confirmed using DNA in *situ* polymerase chain reaction (PCR). Of note, HIV-1 RNA and DNA were also detected in renal epithelia from several patients with undetectable viral loads, suggesting that renal cells may act as a reservoir for HIV-I (15). Additional evidence for a renal reservoir of HIV-1 was provided by a case report of a patient who developed HIVAN with acute HIV-I infection. Treatment with highly active antiretroviral therapy resulted in resolution of clinical and pathologic signs of the disease. However, renal epithelial expression of viral mRNA did not change following treatment (3). Marras et al. used laser-capture microdissection to remove infected renal tubular cells from 2 patients. Phylogenetic analysis of gp120 DNA sequences obtained from these cells and peripheral blood mononuclear cells from the same patients revealed evidence of tissue-specific viral evolution, suggesting that renal epithelial cells are able to support full viral replication (24). The mechanism of viral entry into renal epithelial cells is still unknown. CCR5 and CXCR4 are coreceptors to CD4 that mediate HIV-1 entry into lymphocytes. These receptors have not been demonstrated on renal epithelial cells *in vivo* (25).

Podocytes are the visceral epithelial cells that surround glomerular capillaries, forming an important part of the glomerular filter apparatus. They are terminally differentiated, quiescent cells that do not proliferate even in the setting of most glomerular diseases and podocyte injury. However, the collapsing glomerulopathy of HIVAN is characterized by marked podocyte dedifferentiation and proliferation. Studies have shown that HIV-1 infection leads to loss of differentiation markers in podocytes such as WT-1, synaptopodin, podocalyxin and common acute lymphoblastic leukemia antigen (CALLA). There is also an increase in proliferation markers such as Ki-67 and alterations in cell cycle regulators such as p27 and p57 (26 – 28). Conditionally immortalized HIV-1 transgenic podocytes proliferate *in vitro* in the presence of HIV-1 gene expression (29, 30).

Tubular microcyst formation is often the most prominent aspect of HIVAN pathology. Increased apoptosis and proliferation of tubular epithelial cells are seen in HIVAN (23, 26, 31). Microcyst formation and HIV-1 infection have been demonstrated in multiple segments of the nephron. One possible explanation for the development of microcystic disease in HIVAN is that HIV-1 infection initiates cyst formation by inducing proliferation of tubular epithelial cells. However, as the microcystic tubular epithelium becomes thin and atrophic, HIV-I expression decreases, thereby decreasing epithelial proliferation and arresting cyst development at the microcystic stage (20).

Transgenic mice models have also been used to determine which HIV-I genes are necessary to cause renal disease. HIV-I encodes 9 different gene products, including the structural proteins gag, pol and env, regulatory proteins tat and rev, and accessory proteins vif, vpr, vpu, and nef. Studies using transgenic mice have implicated both nef and vpr in HIVAN pathogenesis (32, 33).

In vitro studies have confirmed the importance of nef in HIVAN pathogenesis. Infection of murine podocytes with an HIV-1 proviral construct with stop codons introduced at nef causes proliferation, anchorage-independent growth, loss of podocyte differentiation markers and increases in podocyte proliferation markers. On the other hand, infection of murine podocytes with full-length HIV-1 containing mutated nef fails to recapitulate the phenotypic changes found in HIVAN (29, 34, 35). Nef has multiple functional domains that can interact with cellular signal transduction molecules. Recent work has demonstrated that nef exerts its phenotypic changes in podocytes by activating the Src-Stat3 and Ras-c-Raf-MAPK 1,2 pathways (33).

Genetic Susceptibility to HIVAN

The apparent predisposition of patients of African descent to develop HIVAN suggests that host genetic factors are important determinants of whether an HIV-seropositive patient will develop HIVAN. Mice display a similar genetic predisposition to HIVAN. Certain mouse strains are susceptible to developing a HIVAN phenotype in the presence of an HIV-1 transgene, whereas other strains are resistant. Gharavi et al. used genome-wide linkage analysis to map genetic loci that are associated with the development of the HIVAN phenotype in mice (36). Several candidate loci have been identified, and attempts to determine the responsible genes within these loci are underway.

Treatment

HAART

The most compelling evidence for the efficacy of HAART in preventing progression of HIVAN to ESRD is that in the United States, the annual number of new patients whose ESRD is caused by "AIDS nephropathy" (the term used by the USRDS to identify patients with HIV-related renal disease) has remained relatively steady since 1995. This is in contrast to the steady rise in prevalence of HIV/AIDS in the general population, and the dramatic decrease in HIV/AIDS-related mortality in the U.S. This discrepancy suggests that HAART is indeed effective in preventing progression to end-stage renal failure in HIVAN patients. In a retrospective cohort study by Szczech et al. of 19 patients with HIV-related renal disease, patients receiving protease inhibitors had a significant reduction in the rate of decline of renal function (37). In one case report Winston et al. documented the resolution in clinical and pathological signs of HIVAN 15 weeks after the institution of HAART (3).

HAART may also prevent the development of HIVAN in at-risk groups. Lucas et al. evaluated a cohort of 3,976 at-risk patients in the Johns Hopkins HIV clinic database from 1989 to 2001. They identified 135 cases of HIVAN based on either clinical or pathological criteria. HAART was associated with a 60% reduction in risk for developing HIVAN (5).

ACE Inhibitors

There are several small studies suggesting a beneficial effect of ACE inhibitors on HIVAN. Wei et al. studied 44 patients with biopsy-proven HIVAN with serum creatinine < 2.0 mg/dL (0.7 – 1.4 mg/dL). All patients were offered treatment with the ACE inhibitor fosinopril. Twenty-eight patients assented to treatment with fosinopril 10 mg once daily, and the 16 patients who refused treatment acted as controls. After 5.1 years, all the patients on fosinopril had maintained stable renal function, whereas all patients in the control group were on dialysis. The study was limited by self-selection among the patients and concurrent medications were not controlled (38). Overall, the studies suggest that ACE inhibitors are beneficial for patients with HIVAN. However, a need remains for prospective studies to delineate the optimal role of ACE inhibitors in HIVAN.

Prednisone

Several studies have evaluated the efficacy of prednisone in the treatment of HIVAN. Smith et al. reported a series of 20 patients with advanced HIVAN who were treated with oral prednisone. In 17 patients, serum creatinine decreased significantly; but relapse was common after cessation of therapy. Six patients developed infectious complications while on steroid therapy (39). Eustace et al. evaluated a cohort of 21 patients with biopsy-proven HIVAN, 12 of whom were treated with prednisone. Multivariate analysis revealed that treatment with prednisone was associated with an odds ratio of 0.2 for developing ESRD. Infectious complications were not significantly elevated in the steroid treatment group; but once again relapse was common (40). Given the small size and lack of randomization of these studies, further evidence is needed before exposing patients with advanced HIV-1 infection to the potential side effects of prednisone.

Dialysis and Transplantation

In spite of a theoretical concern that hemodialysis may enhance white blood cell release of cytokines, thereby increasing viral replication, USRDS data does not show a survival advantage for peritoneal dialysis over hemodialysis (41). Unfortunately, survival of HIV-1 seropositive patients requiring renal replacement therapy is poor compared to HIV-1 seropositive patients not on dialysis and non-HIV-1 seropositive dialysis patients (42). With decreased morbidity and mortality in HIV-1 seropositive patients, kidney transplantation is now more frequently considered and performed by some transplantation centers. Roland et al. presented preliminary data of HIV-1 seropositive patients without a history of opportunistic infections, with CD4 T cell counts greater than 200 cells/mm^3 (480 – 1700 cells/mm^3) and with undetectable viral loads, who underwent solid organ transplantation. The patients were followed for only approximately 1 year, and data suggest that CD4 cell counts and plasma HIV RNA level suppression can be maintained in the setting of post-transplant immunosuppression in suitable patients. Patient and graft survival rates were similar to 1-year survival rates in the United Network for Organ Sharing (UNOS) database (43). A multicenter prospective study is currently underway to determine the safety and efficacy of renal transplantation in HIV-1 seropositive patients with ESRD.

Conclusion

HIVAN is the most common cause of chronic renal failure in HIV-1 seropositive patients and is especially prevalent among patients of African descent. Though HAART has dramatically reduced mortality of patients with HIV/AIDS, the incidence of ESRD due to HIVAN has remained stable and is likely to increase. HIV-1 infection of the renal epithelium is a critical component of HIVAN pathogenesis and also represents an important reservoir in which the virus may persist despite a lack of detectable virus in plasma. The efficacy of antiretrovirals, ACE inhibitors, and prednisone has been evaluated in small retrospective studies, but larger prospective studies of their value for the prevention and treatment of HIVAN are urgently needed.

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Peripheral Ischemia Caused by Paradoxical Embolization:

An Underestimated Problem?

Beate Hugl, M.D.[1], Peter Klein-Weigel, M.D.[2], Lydia Posch, M.D.[1], Andreas Greiner, M.D.[1], and Gustav Fraedrich, M.D.[1]

Abstract

Although a patent foramen ovale (PFO) is often found in younger patients with transient ischemic attacks or stroke, paradoxical embolization through PFO is rarely considered as a cause of acute limb ischemia.

We report a single-center experience of 5 consecutive patients with limb-threatening ischemia due to paradoxical embolization within a one-year period. All patients were treated by catheter thrombectomy and long-term oral anticoagulation after surgery.

The fact that the 5 embolectomies made up 10% of all embolectomies performed in our center during this time interval may indicate that the role of paradoxical embolization is still underestimated in peripheral embolic disease.

Key Words: Paradoxical embolism, patent foramen ovale, peripheral ischemia.

Introduction

A PATENT FORAMEN OVALE (PFO) is often found in younger patients with stroke, (1 – 3). Although the embolic source in the venous system and the conditions for the development of a right-to-left pressure gradient enabling thrombus material to pass through the septal defect often remain unclear retrospectively, it is commonly accepted that paradoxical embolism is the pathophysiologic linkage between PFO and cerebral ischemia (3). In contrast to stroke, paradoxical embolization is still rarely considered as a possible cause of acute limb ischemia and might therefore be underestimated (4 – 7). We present a series of patients with PFO and acute limb ischemia encountered in a one-year period, presumed to be due to paradoxical embolization. We also review the literature on diagnostic procedures and therapeutic options to prevent recurrences.

Case Reports

Case 1

A 78-year-old woman was admitted with acute ischemia of the right arm and treated with emergency catheter embolectomy of the distal brachial and cubital arteries. Electrocardiogram (ECG) recordings documented constant sinus rhythm. Transesophageal echocardiography did not reveal a cardiac source of embolization but showed tricuspid regurgitation in the presence of pulmonary hypertension (systolic PAP at least 45 mm Hg). The patient was finally discharged on oral anticoagulation therapy, but had to be readmitted three days later with acute ischemia of the right leg despite adequate anticoagulation (INR 3). Duplex sonography identified an embolic occlusion of the popliteal artery (Fig. 1). Aspiration embolectomy failed and surgical embolectomy had to be performed. The postoperative course was complicated by a retroperitoneal hematoma, requiring surgical treatment, and the onset of acute dyspnea. After recovery, a more extensive diagnostic evaluation at this point identified a 10 mm PFO with spontaneous right-to-left shunt (Fig. 2, Table 1). Furthermore, a clinically asymptomatic right popliteal vein thrombosis was

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[1] Department of Vascular Surgery, University Hospital, Innsbruck, Austria and [2] Department of Physical and Rehabilitative Medicine, and Angiology, DRK-Kliniken Berlin, Germany.

Address all correspondence to Beate Hugl, M.D., Department of Vascular Surgery, University Hospital, Anichstrasse 35, A-6020 Innsbruck, Austria; e-mail: beate.hugl@uibk.ac.at

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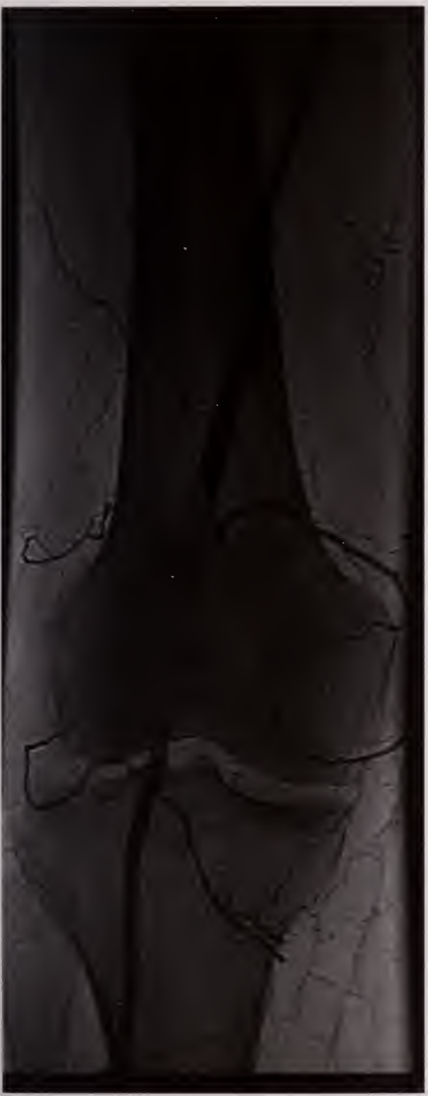

Fig. 1. Arteriogram demonstrating embolic material in the right popliteal artery.

diagnosed by compression ultrasound and multifocal pulmonary artery embolization by spiral CT scan. Because pulmonary embolism occurred despite sufficient anticoagulation, a vena cava filter was implanted. Closure of the PFO was not performed, considering the advanced age of the patient and possible associated complications. Further follow-up was uneventful.

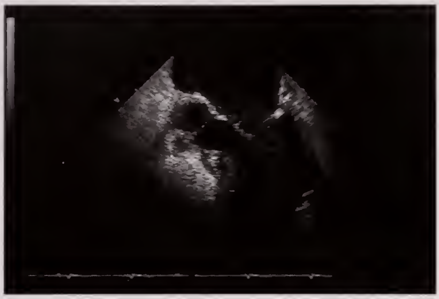

Fig. 2. Transesophageal echocardiography demonstrating a right-to-left shunt.

Case 2

A 64-year-old man with sudden onset of severe leg pain three weeks prior was admitted with decompensated ischemia of the left leg. Duplex sonography and angiography revealed a thrombotic occlusion of the popliteal and distal femoral arteries, as well as a partial occlusion of the calf arteries in the absence of atherosclerotic wall lesions. Catheter embolectomy of the calf arteries was performed successfully, but the femoropopliteal artery rethrombosed. Therefore, a femoro-tibial vein bypass was implanted. Perioperative ECG recordings documented ventricular extrasystoles but constant sinus rhythm. Transesophageal echocardiography revealed a 6 mm PFO but no aneurysm (Table 1). Spontaneous right-to-left-shunt could not be documented, nor could a deep vein thrombosis. Oral anticoagulant therapy was started and had to be maintained to prevent bypass failure.

Case 3

An 83-year-old women presenting with limb-threatening ischemia of the right leg was admitted for catheter embolectomy of the iliacal, femoral and popliteal arteries. Because of the long-lasting ischemia (8 hours), subcutaneous medial and lateral fasciotomy of the lower leg also had to be performed. Serial ECG recordings documented a constant sinus rhythm. Transesophageal echocar-

TABLE 1

Results of Transesophageal Echocardiography in all 5 Cases (No Patient Had an Increased Membrane Mobility)

Case	Size PFO	Aneurysm	Spontaneous	Pulmonary R-L Shunt	DVT Hypertension	PE
1	10 mm	N	Y	Y	Y	Y
2	6 mm	N	unknown	N	unknown	unknown
3	unknown	Y	Y	Y	unknown	Y
4	unknown	N	Y	Y	Y	Y
5	unknown	N	N	N	N	N

DVT = deep venous thrombosis; PE = pulmonary embolism; N = no; Y = yes; R-L = right to left; PFO = patent foramen ovule.

diography detected an aneurysm of the atrial septum and a PFO with spontaneous right-to-left shunt (Table 1). In the right pulmonary artery near the main truncus, a thrombus (25 × 10 mm) could be seen; it led to a luminal occlusion of 25%. However, the right ventricle was dilated and had normal function. Due to unfavorable conditions, pulmonary artery pressure could not be determined and deep vein thrombosis could not be identified by duplex sonography. Postoperatively, the patient received continuous unfractionated heparin followed by long-term warfarin therapy. Closure of the PFO was not performed, because of the pulmonary embolism and the advanced age of the patient.

Case 4

A 73-year-old man was admitted with ischemic paresthesia of the right lower limb of 3 days' duration and increasing dyspnea over the previous month. Clinically, the patient presented with a cold leg and no femoral or popliteal pulse. Two hours later, an acute artery occlusion of the left arm occurred, requiring urgent catheter embolectomy. Ischemia was caused by an extensive embolus of the subclavian and brachial arteries. Postoperative dyspnea and tachycardia with multiple extrasystoles occurred, and the right leg became paralyzed. Duplex sonography detected occlusion of the right superficial femoral artery and fresh emboli in the profunda femoral artery. Consequently, catheter embolectomy of the common, superficial and profunda femoral arteries was performed, successfully, followed by a patch angioplasty of the femoral artery. Transesophageal echocardiography identified a PFO with spontaneous right-to-left-shunt and hypertrophy of the left ventricle, but no aneurysm (Table 1). Multiple pulmonary emboli on both sides and a deep vein thrombosis (popliteal vein) were diagnosed by spiral CT. Oral anticoagulation was started to avoid further embolic events.

Case 5

A 62-year-old woman was admitted with acute ischemia of the left arm. The patient complained of sudden onset of arm pain followed by paresthesia. Duplex sonography revealed embolic occlusion of the distal axillary and brachial arteries. Transbrachial catheter embolectomy was performed successfully. Six months earlier, a PFO with a spontaneous left-to-right shunt had been diagnosed by transesophageal echocardiography, but there was no proof of intracardial thrombus or aneurysm (Table 1). At that time, treatment with digitalis and short-term warfarin therapy was started because of paroxysmal atrial fibrillation. Pre- and postoperative ECGs documented a constant sinus rhythm, and cranial CT detected a hypodense cortical area without neurological correlation. Warfarin therapy was reintroduced.

Discussion

Paradoxical embolization was first described by Cohnheim in 1877 (8). In most cases the passage for the thrombus from the venous into the arterial circulation was found to be a patent foramen ovale (9).

PFO has often been reported in patients with transient ischemic attacks (TIA) or stroke, and there is increasing evidence that a causative relationship exists between these two pathologies, especially in younger patients with sinus rhythm and normal cerebral arteries (1–3, 10). In contrast to cerebral embolization, PFO has rarely been reported in patients with peripheral ischemia.

Paradoxical embolization was found in 14 of 406 cases of arterial embolism in the series published by AbuRahma and Downham (6), which covered an 8-year period, and in 7 patients in the analysis of hospital records from 1970–1993 by Chaikof et al. (5). More recently, Travis et al. (7) published their data of a 10-year period from 1989–1999, in which paradoxical embolization accounted for only 13 cases of acute arterial occlusion, including 3 cerebral and 2 bowel infarctions. All of these series were retrospective analyses that included a high percentage of cases with uncertain embolic sources and incomplete work-up.

Our single-center experience of 5 consecutive patients presenting within less than 12 months with limb-threatening peripheral emboli of cryptogenic origin and a final diagnosis of PFO might indicate that the role of paradoxical embolization is still underestimated in peripheral embolic disease. This argument is strongly supported by the fact that the 5 embolectomies in our series made up about 10% of the embolectomies performed in our center within the time period between August 2001 and June 2002. On the other hand, the coincidence of a PFO and a peripheral embolic event in the same patient does not necessarily mean that there is a causal relationship (2). PFO was reported to be present in up to 25–35% of the general population at autopsy and in 10–18% in transthoracic contrast echocardiographic studies (9, 11), whereas Fisher et al. (12) reported an incidence of 9.2% in 1,000 consecutive patients who underwent transesophageal echocardiography for various indications.

Diagnosis of systemic embolization due to PFO therefore requires three conditions: (a) the presence of a thrombus through the PFO or the diagnosis of a thromboembolic source in the venous system; (b) the presence of a transient atrial pressure gradient allowing right-to-left transition of the embolic material; and (c) exclusion of a left-sided embolic source (10). In peripheral embolization, one might additionally require that the size of the PFO be large enough to allow passage of clots capable of blocking the lumen of the typically affected peripheral arteries, i.e., the popliteal and brachial arteries. Thomson and Evens (9) found PFO of 0.2–0.5 cm in 29% and PFO of 0.6–1.0 cm in 6% of their autopsies, whereas an average PFO size of 1.23 cm was reported by Bridges et al. in their series (13).

It is easy to detect a right-to-left shunt with contrast transcranial Doppler sonography of the middle cerebral artery, especially when Valsalva's maneuver is used for an increase in right atrial pressure (14, 15). Nevertheless, only transesophageal multiplane contrast echocardiography (transesophageal echocardiography) is capable of determining the exact morphological and functional characteristics of an atrial defect (16, 17). Transcranial Doppler sonography might therefore be used as a screening test; however, confirmation and specification by transesophageal echocardiography is still necessary (18).

As with stroke, morphologic and functional characteristics of the PFO can help to identify subgroups of patients at higher risk for paradoxical embolization and recurrences after a first event. These factors include PFO > 4 mm, detection of a spontaneous right-to-left shunt, large shunt volume, increased membrane mobility, and concomitant atrial septal aneurysm (17, 19–21).

A PFO > 4 mm was confirmed in only 2 cases of our series, but routine transesophageal echocardiography examinations in the series focused more on the detection of a PFO and on the identification of an interatrial shunt than on exact measurements of PFO size. Spontaneous right-to-left shunt was detected in 3 patients. In case 3, echocardiography also revealed a septal aneurysm. Pulmonary hypertension due to pulmonary embolism was detected in all three patients with a right-to-left shunt, and in all of these patients, deep venous thrombosis of the legs was confirmed by compression ultrasound. On the other hand, detection of deep venous thrombosis can be difficult, especially when diagnostic measures are performed late in the course of the illness (22). Even bilateral phlebographic examination immediately after stroke was reported to be successful only in about 10% of the patients (23). More extensive work-up, including bilateral duplex sonography, and magnetic resonance tomography of the pelvic veins, can increase the detection rate of venous thrombosis in the case of pulmonary embolism (24, 25); however, data on PFO are missing.

Obviously, the strict diagnostic criteria for paradoxical embolization formulated by Johnson (10) guarantee high specificity but lack sensitivity. As applied to our patients, the diagnosis of paradoxical embolization could be confirmed in only 3 of the 5 cases. From a more practical viewpoint, the diagnosis of paradoxical embolization might also be permitted in the case of confirmed PFO and the carefully elaborated exclusion of other thromboembolic causes (4, 26), which was the case in our remaining patients. On the other hand, the latter approach does not always allow distinction between a "causative" PFO and an "innocent" PFO (2), as might best be illustrated by case 5 of our series.

Valid data to determine the exact risk of recurrences in case of peripheral embolization due to paradoxical embolization are missing. In stroke, the Lausanne and the French study groups reported recurrences of 3.4–3.8% for stroke and 1.2–1.9% for transient ischemic attacks in patients treated with salicylic acid (26, 27). Low recurrence rates were also confirmed by a recent meta-analysis (28). Homma et al. were able to show that medical treatment can safely prevent recurrences even in cases with PFO and septal aneurysms (29). In contrast to this data, 9–11% high-risk patients were formerly reported to suffer from recurrent cerebrovascular events annually (26, 30, 31).

Long-time results of surgical closure of the PFO are limited to small, uncontrolled series, for whom studies have reported recurrent cerebral events in 0 – 19.5% of those treated (30, 32, 33). In their retrospective analysis of 91 patients, Dearani et al. (33) found no cerebral infarctions during a 4-year follow-up, but identified TIAs in 16% of the surgically treated patients without evidence of a residual shunt, indicating incorrect diagnosis or additional embolic sources in many patients.

Despite uncertain long-term results, percutaneous PFO closure as a minimally invasive procedure is now acceptable (13, 34 – 42). Bridges et al. (13) reported four TIAs in 34 patients, and 6 residual shunts were identified within 4 – 8 months after the intervention. In an uncontrolled study by Wahl et al. (36) dealing exclusively with PFO, the technical success rate was 98% and the complication rate 10%. During the follow-up, residual shunting was detected in 27% of the patients. Freedom from recurrence of the combined endpoint of TIA, ischemic stroke, and peripheral embolization in the study of Sievert et al. (38), dealing with 281 septal defects, was 95.7% at one year and 94.1% at 3 years. These mid-term-results were confirmed by others concentrating on PFO only (35, 37, 40, 42). Braun et al. (41) even published a 0% recurrence rate of stroke and peripheral emboli in 246 patients with percutaneous PFO closure over an average of 15.1 months and a TIA rate of only 1.7% within the same time period (Table 2).

Nevertheless, neither surgical nor percutaneous closure can treat or prevent pulmonary embolism in cases of deep venous thrombosis. Therefore, antithrombotic therapy is still considered to be the first-line therapy in cases with venous thromboembolism (28) (Table 3). All of our patients received unfractionated heparin followed by acenocoumarol with a target INR of 2 – 3. In one of our cases, a vena cava filter was additionally implanted because pulmonary embolism occurred despite satisfying anticoagulation therapy. Patients in whom venous thromboembolism cannot be confirmed can be treated with aspirin alone. A recent subanalysis of the Warfarin-Aspirin Recurrent Stroke Study stated that with either medical therapy, the presence of PFO in stroke patients did not increase the chance of adverse events, regardless of PFO size or the presence of atrial septum aneurysm (29).

Summary

According to our experience, it must be assumed that paradoxical embolization through PFO

TABLE 3

PFO: Recommended Therapeutic Approach—Consider as First-Line Therapy

oral anticoagulation	in all cases with proven DVT or PE or concomitant disease requiring oral anticoagulation
ASA	in all other cases with first event
percutaneous PFO closure	in all patients with contraindications for medical therapy in all patients with recurrences under medical therapy in all high-risk-patients*

*one of the following: large PFO, spontaneous R-L-shunt, increased membrane mobility, atrial septal aneurysm.
DVT = deep venous thrombosis; PE = pulmonary embolism; ASA = acetylsalicylic acid.

TABLE 2

Technical Success, Early Complication Rates and Embolic Recurrences in Trials with >100 Patients Dealing with Percutaneous Closure of PFO.

author	n	Technical Success	Device Migration	Pericardial Tamponade	Follow-up	TIA	Stroke	Peripheral Embolization
Onorato et al. (42) (2003)	256	100%	0%	0.4%	1.6 y	0.4%	0%	0%
Martin et al. (40) (2002)	110	100%	0.9%	0.9%	2.3 y	0.9%	0.9%	0%
Braun et al. (41) (2002)	276	100%	0.7%	0%	1.3 y	1.7%	0%	0%
Wahl et al. (36) (2001)	132	98%	3%	0.8%	1.8 y	4.5%	0%	1.5%
Sievert et al (38) (2001)	281	100%	0.7%	0%	1 y	2.5%	0.7%	0%

n = patient number; y = year(s); TIA = transient ischemic attacks.

is still underestimated in peripheral embolic disease. Therefore, all cryptogenic embolizations should undergo multiplane contrast transesophageal echocardiography or at least contrast transcranial Doppler sonography of the middle cerebral artery as a screening test. Once a PFO has been confirmed, bilateral compression ultrasound or bilateral phlebography of the legs should be performed. Pulmonary embolism as a cause of right atrial pressure increment is best detected by lung scintigraphy or CT angiography. Anticoagulant therapy with a target INR of 2–3 should be started in all cases with proven venous thromboembolism. Aspirin alone might be equally effective in preventing recurrences in cases without detection of a thromboembolic source. Percutaneous closure of the PFO can be considered as first line therapy in high-risk patients as well as in patients at risk for anticoagulant therapy. Percutaneous closure of the PFO should also be performed in cases of recurrences most likely related to paradoxical embolization despite adequate antithrombotic or antiplatelet therapy, or in patients who have contraindications for these drugs.

To optimize the therapeutic approach in symptomatic PFO, randomized controlled studies directly comparing medical versus interventional therapy are urgently needed (43).

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Chiropractic Sympathectomy:

Carotid Artery Dissection with Oculosympathetic Palsy after Chiropractic Manipulation of the Neck

Amir M. Khan, M.D., Nissar Ahmad, M.D., Xe Li, M.D., Mark A. Korsten, M.D., and Alan Rosman, M.D.

Abstract

The association between carotid artery dissection and oculosympathetic palsy is well-known. However, the occurence of this combination with chiropractic manipulation of the cervical neck is rare. We describe the case of a 54-year-old Caucasian American male who underwent cervical manipulation for neck pain. The following day he noticed drooping of his left eyelid, with an unequal pupil size. Imaging later confirmed carotid artery dissection. Only three previous cases (one from the United States), of an association between carotid artery dissection and chiropractic sympathectomy (oculosympathetic palsy after chiropractic manipulation of the neck) have been reported. Pictures of the oculosympathetic palsy, computed tomography of the head and magnetic resonance imaging of the dissection are presented.

Key Words: Chiropractic manipulation, carotid artery dissection, sympathectomy, oculosympathetic palsy.

Introduction

The association between cervical manipulation and carotid arterial dissection has been reported several times in the literature, with increasing frequency over the last twenty years. This coincides with the increasing popularity of chiropractic treatment (1, 2).

Although the general consensus is that the overall complication rate from cervical manipulation is low, growing controversy has occurred over the risks and benefits of manipulation of the neck (3). Fatal complications have been described in the literature, and complications have been reported with chiropractic cervical manipulation (4–7).

This report documents a case of oculosympathetic palsy with carotid artery dissection after chiropractic manipulation of the neck. Only three previous cases have been reported in the literature.

Case Report

A 56-year-old Caucasian male with medical history of borderline hypertension (managed without medications) had back neck pain for three days prior to his admission.

The patient went to see a chiropractor three days prior to admission to the hospital, for treatment of this neck pain. This pain was 8/10 in intensity, dull to throbbing in character, located at the left para-cervical level, radiating to the upper back of his neck and aggravated when he moved his neck sideways. After chiropractic treatment of this pain with repeated neck movements, the pain eased only slightly.

The following morning, he woke up to find his left eyelid drooping. That evening his wife noticed that his pupils were unequal in size, the right one larger than the left. There was minimal blurring of his left eye vision, which was transient, lasting a few hours and resolving spontaneously. By this time, his neck pain had improved markedly.

He denied any other symptoms, such as weakness, numbness, tingling and changes in his speech, bowel or bladder functions.

On examination, both pupils were reactive to light and accommodation, with the right one reacting to light from 3–2.5 mm and the left one from

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From the Medical Program, Veterans Affairs Medical Center, Mount Sinai School of Medicine, Bronx, NY.

Address all correspondence to Dr. Amir M. Khan, 7A11, VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468; email: dramirkhan@hotmail.com

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1.5 – 1 mm. Mid-position lid droop of the left eye was also noticed (Fig. 1).

Mild para-spinal tenderness was noticed on the back of his left lower neck. According to neurological examination, the cranial nerves, face and extremities were normal. Plain x-rays of the cervical spine and an initial admission non-contrast computed tomography (CT) of the head (Fig. 2) also showed normal features. However, results of the magnetic resonant imaging (MRI), (Figs. 3 and 4) revealed left carotid artery dissection at the levels of C1 and C2 with weak intensity of the left internal carotid artery.

The patient was admitted to the hospital and anticoagulated with heparin, which was later changed to warfarin. He was discharged without any further complications. He remained asymptomatic during his three-month follow-up, with resolution of his dissection revealed by repeated MRI.

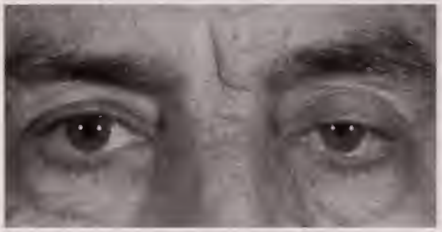

Fig. 1. Left eye droop of the patient, with left pupil constricted more than the right.

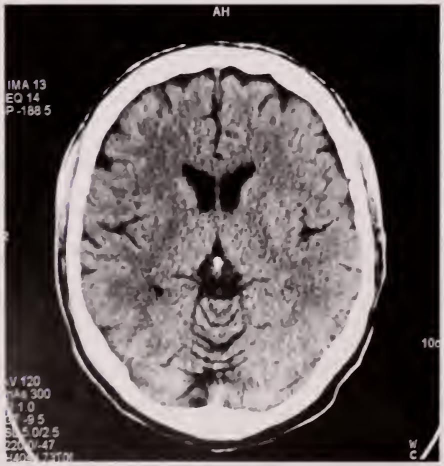

Fig. 2. CT scan of the head with normal findings.

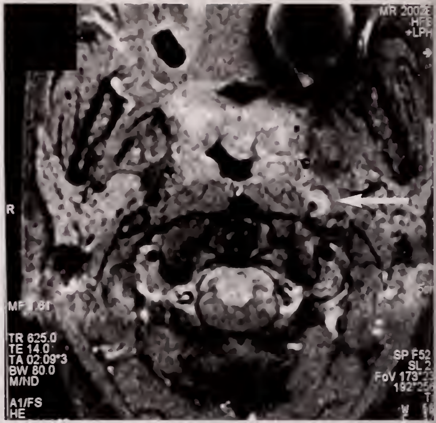

Fig. 3. MRI cross section showing left-carotid dissection (arrow).

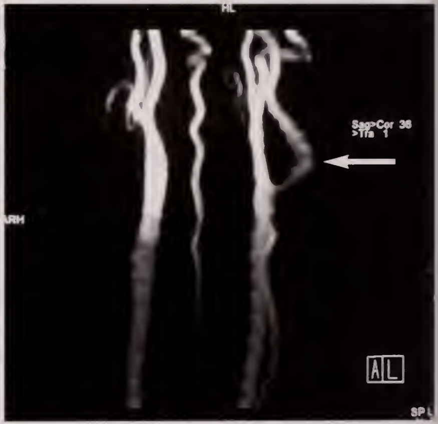

Fig. 4. MRI sagittal section showing left-carotid dissection (arrow).

Discussion

Carotid artery dissection typically presents with pain on one side of the face or neck and with partial Horner's syndrome (oculosympathetic palsy) (8 – 12). The sympathetic lesion of oculosympathetic palsy is post-ganglionic. This dissection, if progressive, results in cerebral or retinal ischemia. Recognition of this triad (pain, Horner's syndrome and ischemia) is critical, though it occurs in only one-third of the patients. Prompt recognition can lead to early diagnosis, treatment and prevention of progression of symptoms (13, 14).

The sympathetic pathways are composed of three neuron chains. The first-order neuron (hypothalamus to level of C8–T2) synapses with the second-order neuron (sympathetic chain in the neck to the level of C2 in the posterior carotid sheath). From here, the third order neuron ascends along the internal carotid artery into the skull and eye, ultimately dilating the papillary sphincter muscles. The cervical sympathetic trunk is embedded in the posterior carotid sheath, a condensation of deep cervical fascia with the internal jugular vein, vagus nerve, and common and internal carotid arteries. It is here that the sympathetic chain is vulnerable to injury from the carotid artery.

Carotid artery dissection can be spontaneous or it can be caused by trauma. It is characterized by damage to the tunica media by an intimal tear (4, 12–17). Brandt and Grond-Ginsbach showed it to be more prevalent in individuals with abnormal collagen bundles on dermal biopsies and that it had a genetic predisposition (18). Others have shown that vomiting and blunt injury can cause carotid dissection (19, 20).

Daniel Palmer, in 1895, reported one of the first beneficial effects of cervical manipulation when he described the resulting partial relief of a patient's deafness (21). It was not until 1927 that the first case of vascular accident was described with cervical manipulation, and in 1945 the first case of spinal cord injury was reported (22–25). Although cervical manipulation is generally considered to be safe, complications range from transient discomfort (20, 26) to dissection of the vertebral artery (27) or internal carotid artery (3), stroke (28, 29) and even death (2, 30–33). Chiropractic manipulation of the cervical spine is associated more frequently with vertebral artery dissection than with cervical artery dissection (5, 31, 34).

Grayson, in 1987, reported the first case of Horner's syndrome after manipulation of the neck (35). Since then, two other cases have been reported (36, 37). In the second and third cases the symptoms of the patients were noticed several days after chiropractic manipulation of the neck. However, in our case and Grayson's case, the resulting sympathectomy (chiropractic sympathectomy) was noticed the following day, suggesting its immediate association with the chiropractic manipulation.

To prevent thromboembolic complications, anticoagulation with intravenous heparin followed by warfarin is usually recommended for cervical artery dissection, unless there are contraindications (13, 14, 17). No randomized trials have been reported for the validity of such treatment or for comparing antiplatelets with anticoagulation (38). Still the target range of international normalization ratio (INR) is considered between 2 and 3, with treatment for three to six months. Others suggest repeating the magnetic resonance angiogram after three months and looking for luminal irregularities. Further treatment with anticoagulation can be continued or a switch to antiplatelet therapy can be made subsequently. Surgery with balloon angioplasty or stenting is recommended in cases of failed medical treatment (39, 40).

Conclusion

Patients, chiropractors and physicians should all be aware of potential neurological adverse outcomes following cervical manipulation. Early recognition of these adverse effects is critical and prompt treatment important. We also suggest that patients with neck pain be examined and neuro-imaged in order to exclude possible underlying pathologies before receiving any manipulation of the neck.

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Book Review

Blueprints Q&A Step 2 Surgery, 2nd edition

Edward W. Nelson, Malden, MA:
Blackwell Publishing; 2005.
169 pp. $17.95.
ISBN: 1-4051-0393-0

and

Blueprints Q&A Step 3 Surgery, 2nd edition

Edward W. Nelson, Malden, MA:
Blackwell Publishing; 2005.
179 pp. $17.95.
ISBN: 1-4051-0398-1

THE SECOND EDITIONS of Blueprints Q & A Step 2 and Blueprints Q&A Step 3 Surgery are up-to-date reviews of the field of surgery, intended to prepare medical students and residents for the USMLE Step 2 and Step 3 exams. They are books in a series from Blackwell Publishing, which include reviews of pediatrics, psychiatry, obstetrics, and medicine. The format of the book is that of questions and answers, which is probably the most effective way to prepare for these exams.

The authors include a senior faculty member, Edward W. Nelson, and residents, Rafe C. Connors and Stephen J. Fenton, from the Department of Surgery of the University of Utah School of Medicine. Other contributors (called reviewers) come from Utah and other residency programs. The format of the Q & A Step 2 is that of four separate exams (called blocks) with questions, an answer key and detailed explanations. The Step 3 book has a similar format, except that the four blocks are divided into questions relating to a community-based health center, the office, inpatient facilities, and the emergency department.

The questions in both the Step 2 and Step 3 books are comprehensive and cover most areas that would be expected to appear on the Boards as well as in shelf exams. The answers are very helpful and just long enough to help without being too wordy. These books will be of value to both third and fourth year medical students, and to residents who are preparing to take the Boards or other exams.

Gary Slater, M.D.
Department of Surgery
The Mount Sinai Hospital
New York, NY

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3. Couser WG. Glomerular diseases. In: Stein J, editor. Internal medicine. 2nd ed. Boston: Little Brown; 1987. pp. 834–861.

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THEME ISSUE

Issues in Medical Ethics

Special Challenges of Emergency Medicine

Rosamond Rhodes, Lynne Richardson, and Daniel A. Moros, guest editors

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Introduction

ROSAMOND RHODES, PH.D.
Professor of Medical Education
Director, Bioethics Education

LYNNE RICHARDSON, M.D.
Associate Professor of Emergency Medicine

DANIEL A. MOROS, M.D.
Associate Professor of Neurology

Issues in Medical Ethics:

Special Challenges of Emergency Medicine

"But it's an emergency!" This is a reason commonly offered—and accepted—as justifying an action that would otherwise be condemned as a violation of the rules of ordinary morality. That the building is on fire warrants breaking doors and windows, even though destruction of another's property is usually prohibited. That a child is in danger of drowning warrants the unauthorized use of another's property in a rescue effort, even though doing so is otherwise counted as theft. That someone is in harm's way can justify pushing the person to the ground to avoid the danger, even though the identical action would be an assault had there been no threat. In sum, whether or not we specifically acknowledge the differences, we generally agree that the rules we live by may and sometimes must be broken when we confront an emergency.

Emergency situations can be important enough to justify departures even from the normal and customary ethical standards of medical practice.

In routine medical practice, physicians are supposed to elicit their patients' informed consent before performing tests or initiating treatments. And a patient who refuses a test or intervention should not have to undergo it. Yet sometimes, in a medical emergency, physicians cannot stop to provide all of the relevant information required for an informed decision. Sometimes, under emergency circumstances, patients are not even capable of expressing consent or refusal.

Under normal circumstances, when patients lack the capacity to make their own treatment decisions, physicians invest time and effort to identify an appropriate surrogate who will make decisions on behalf of the patient. When no obvious surrogate is available, physicians will even ask the courts to appoint a legal guardian for making medical decisions. Frequently, however, emergency physicians cannot delay treatment in order to identify an appropriate surrogate, and there are even urgent circumstances when physicians cannot wait to elicit informed consent to treatment from a previously identified surrogate decision maker.

Confidentiality is an important and broadly acknowledged principle of medical ethics. Without the assurance that patient information will be closely guarded and not shared with others, patients would normally be reluctant to divulge personal information, particularly information about behavior that might be shameful or illegal. Yet it could be crucial for a physician to have such information, in order to make the correct diagnosis and identify the appropriate course of treatment. So the promise of confidentiality is critically important for the ethical practice of medicine. Nevertheless, when physicians obtain information that signals imminent, significant and avoidable harm to either the patient or another person, they may violate the rule of confidentiality in order to save life.

In the standard practice of medicine, patients are assured that their physicians will act in their interest. Medical students are carefully taught to put their patients' interests before their own and to care deeply about the well-being of each patient; senior clinicians earn the esteem of their peers because of their selfless devotion to their patients' needs. However, in emergencies with large numbers of casualties, where the need for treatment greatly exceeds the available resources for rendering care, the best interests of some patients are sacrificed so that the collective outcome can be optimized. Deliberately setting the interests of some patients aside because they are not likely to survive, regardless of the intervention, or because saving them would require a tremendous investment of very scarce resources, is an accepted part of medical triage. Clinicians who prepare for disasters actually develop triage plans to assure that these principles will be followed.

Clinical research is governed by complex rules designed to assure that people are enrolled in studies only after they have provided their informed consent to serve as research subjects. Yet because some of the injuries and illnesses that befall people also leave them unable to provide informed consent or because they arise under conditions of such urgency that there is no time to elicit informed consent, clinical research under these conditions may require compromising this important principle.

The seventeenth New York Regional Conference on Issues in Medical Ethics at Mount Sinai School of Medicine was held to explore these issues. The conference, entitled "Special Challenges of Emergency Medicine," was jointly sponsored by the departments of Medical Education and Emergency Medicine. Philosophers and emergency medicine physicians presented views on these challenging dilemmas and participated in a lively discussion of the issues.

The following articles are based on presentations from that meeting. First, philosopher Heather J. Gert introduces the broad subject with her paper, "How Are Emergencies Different from Other Medical Situations?" She explains the criteria for classifying a situation as an emergency and offers ways to understand the ethical responses to such conditions. Then, the topic of informed consent and patient refusal of treatment is addressed in "What Part of 'No' Don't You Understand? Patient Refusal of Recommended Treatment in the Emergency Department," by Arthur R. Derse, who is both a law professor and an emergency medicine physician. Physicians Laura G. Iavicoli and Reza Keshavarz both address the kinds of cases that test the limits on confidentiality in the emergency department. Dr. Iavicoli's "Mandatory Reporting of Domestic Violence: The Law, Friend or Foe?" raises questions about the law, the effectiveness of interventions to forestall harm, and the advisability of imposing mandatory-reporting statutes. Dr. Keshavarz's paper, "Adolescents, Informed Consent and Confidentiality: A Case Study," discusses the issues of capacity and trust with regard to adolescent patients.

The two final papers in this issue raise broader policy questions. "Disaster Preparedness and Triage: Justice and the Common Good," by philosopher Robert M. Veatch, explains how funding for disaster preparedness as well as policies for allocating scarce resources during a medical disaster can be regarded as matters of social justice that should be decided according to principles of justice. In her paper, "The Ethics of Research without Consent in Emergency Situations," Lynne D. Richardson, who is both an emergency medicine physician and a health services researcher, explores public policy concerning the ethical conduct of human subject research

Taken together, the papers in this issue provide valuable insight into the ethical problems posed by medical emergencies and their challenge to the ethics of routine medical practice. These papers illustrate how medicine's several important goals can sometimes conflict, and explore how the sacrifice of some may be justified in emergencies. A final point: It is important to recognize and fully value the sacrificed values as well as the values that are honored, in order to be able to justify our decisions and assure that the traditional ethics of medicine have not been set aside.

How Are Emergencies Different from Other Medical Situations?

HEATHER J. GERT, PH.D.

Abstract

Three criteria are necessary for an event to be an emergency: (a) there must be an expectation of serious harm; (b) there must be an expectation that someone can do something to prevent or reduce that harm; and (c) there must be time pressure. Because emergencies are unique in having this set of criteria, standard moral principles, when applied to emergency situations, can require actions that are prohibited in other situations. This can give the impression that there are different moral principles at work in emergencies. This paper argues that this impression is illusory.

Key Words: Moral principles, emergencies, informed consent.

IT IS WIDELY ACCEPTED that there are actions permissible in the emergency department (ED), or in emergency situations, which are not permissible in non-emergency situations. Perhaps most obviously, physicians are more frequently permitted to treat without informed consent in emergency than in non-emergency situations. This sort of observation has tempted some to suppose that standard morality does not apply in emergencies. Normally, physicians are morally required to get informed consent before treating patients; in emergency situations this not always the case. Does this mean that different moral principles are at work?

Part of what I want to show in this article is that, while different moral rules or principles may seem to apply in emergencies, there is an important and fundamental sense in which the applicable rules or principles remain the same. The same basic morality applies in the ED and in all other medical contexts. In fact, the same basic morality applies to any human interactions. But when the same rules are applied in different contexts, different conclusions result. And there are important ways in which emergency contexts are different.

Here are several cases that illustrate the fact that applying the same principle does not always mean doing the same thing: Virtually everyone will agree that it can be appropriate to provide different information to different patients, even when they have precisely the same illness. This is because one patient might prefer to know only what is absolutely necessary, while the other wishes to know as much as possible about his disease. In each case the physician behaves appropriately if she follows the rule: "Give a patient all of the relevant information he wants." If she follows the same rule in both cases, she has done the same thing both times: She gave the patient all the relevant information he wanted. But in another sense she did something different each time—she gave the first patient less information than she gave the second. Or, to take an example from my own profession: Although I apply the same principles to grading all of the papers in a class, and am in that sense doing the same thing as I grade each paper, there is another sense in which I do something different—when I give one paper an A and another a C. Thus, there is no contradiction in saying that the same moral rules apply whether or not the situation is an emergency, while at the same time holding that different actions are permissible in emergencies than in non-emergencies.

In the previous example, what made withholding certain information from a patient morally permissible (and even morally obligatory) in one situation, while doing so in the other would have been

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Address all correspondence to Dr. Heather J. Gert, Associate Professor, Department of Philosophy, MS #4237, Texas A&M University, College Station, TX 77832.

Presented at the Issues in Medical Ethics Conference on "Special Challenges of Emergency Medicine" at the Mount Sinai School of Medicine, New York, NY.

immoral, was a specific morally neutral fact—the fact that the first patient preferred not to receive certain information. Thus, if we want to know why certain types of actions are permissible in emergencies that are not permissible in non-emergencies, it will be useful to consider the morally neutral ways that emergencies differ from non-emergencies. In other words, what makes a particular situation an emergency?

There are three interrelated criteria that a situation must fit in order to be an emergency:

(a) There must be an expectation of serious harm.
(b) There must be an expectation that someone can do something to prevent or reduce that harm.
(c) There must be time pressure.

If a situation is a medical emergency, the expected harm must be of the sort that medicine treats. For instance, if a child is caught in a burning house, that is certainly an emergency. But if the child is rescued quickly, before sustaining any physician harm, then there is no medical emergency. In what follows I will be discussing only medical emergencies.

It seems pretty clear that all three of the listed conditions are necessary in order for something to be an emergency. If a person is going to get a paper cut unless someone acts quickly, that does not constitute an emergency. But neither does seriousness of harm alone constitute an emergency. The fact that a person is in the end stages of renal failure may not constitute an emergency, even though the person is going to die. That is because there may be nothing to be done to prevent her from dying.

Even though all three of these conditions are necessary in order for a situation to be an emergency, in medicine the third condition stands out as the most salient. In the vast majority of medical situations, someone is attempting to prevent or reduce the harm that a patient might otherwise suffer, and these harms are often serious. Emergencies differ because what is going to be done must be done (relatively) quickly. This does not mean that all decisions in emergency situations must be made in a matter of seconds. But it does mean that there is time pressure. There isn't as much time as one would like—time to order tests, convey information to patients, find surrogates, etc.

One might think that another element is necessary for a situation to be an emergency. Aren't emergencies unexpected? Certainly, most of the people who come into the ED did not expect whatever brought them there. They didn't expect the heart attack or the automobile accident. But what makes the ED appropriate for treating emergencies is precisely the fact that the ED staff are prepared to deal with them; this is a place where emergencies are not unexpected. Of course, no one in the ED expected this particular person to arrive with a gunshot wound, or with her appendix about to burst, but they expect that someone will appear with such problems, and therefore they, unlike most other people, are prepared to deal with these emergencies.

A situation can even be an emergency when it is not a surprise to anyone. So, for instance, someone who does not have medical insurance may have a condition that he knows will become acute. He might even know more or less when it will become acute, and the ED staff may be familiar with him and know this too. Despite all of this, when the man presents at the ED, and his malady is acute, this is a genuine emergency. It is an emergency now, even though everyone involved saw it coming, because right now somebody had better do something quickly, or the man will die.

Nonetheless, it is easy to see why we so often think of emergencies as unexpected. In most cases, if we see that something bad is likely to happen, we can and do take measures to prevent it. But sometimes we can't, and sometimes we merely don't. So, even though an event doesn't need to be unexpected to be an emergency, in fact, most actual emergencies are a surprise to someone, and that's the way we are likely to think of them.

I bring this up because it is important to recognize the difference between expected and unexpected emergencies. The fact that a particular emergency is unexpected can be morally relevant (1). In particular, there are many situations in which an emergency's unexpectedness excuses behavior that would otherwise be condemned. This is not usual in the practice of medicine; however, it does happen sometimes.

For instance, consider the case of a young woman interning in a small town, where gunshot wounds are extremely rare. This woman might sincerely but mistakenly believe she knows how to treat a patient who has entered the ED with a gunshot wound, and that calling someone more experienced would take too much time. Even if the intern is mistaken, and the patient suffers or dies because of her decision, she might still be excused. If it does not seem to you that an intern would be excused for making a bad decision in this situation, substitute a situation in which it does seem to you that an intern would be excused. Some of the mistakes made by those who are new to the profession of medicine are excusable. It takes a certain amount of experience to judge these things. She was unprepared, but in this case perhaps it was not her fault. She needed more experience. Because the intern had no reason to expect that she would need to be prepared to deal with this kind of emergency, we do not hold her fully accountable for the bad choice she made because she was unprepared. We might even praise her intentions. But we would not praise her decision or her action. We would tell her that her decision was not the right one, and that she should behave differently next time.

So the intern was excused. This means that even though she did not make a good choice, she should not be held fully morally accountable. The claim that an action is excused is sometimes confused with the claim that it is justified. But unlike a decision or action that is excused, a decision or action that is justified is not a bad one. To say that an action is morally justified is to say that although the action belongs to a category of actions that are usually immoral, in this particular case, circumstances make that action morally permissible (and possibly obligatory). For instance, intentionally killing another person is a type of action that is usually considered immoral. But there are circumstances in which it is justified. For instance, one of the few factors that justify killing a person is that the other person is trying to kill you. Notice that someone who kills in self-defense is not merely excused, he's justified. (I have in mind a situation in which lethal force was necessary to stop the assault. Someone who could have simply run away is not justified in killing in self-defense.)

To say that the person was justified means that we don't merely condone his intention, we condone his decision and his action. And it's the fact that he would otherwise have been killed that justifies that action. We don't say that he shouldn't have killed his assailant, although we understand why he did—as we would if he were merely excused. We do not tell him to behave differently if this situation arises again. Rather, we say that he did the right thing, and we encourage anyone else in the same situation to behave in just the same way. That wasn't what we told the excused intern.

It is worth emphasizing that when we talk about justifying actions we are talking about justifying actions of a type that are usually considered immoral. Most actions aren't of this type, so most actions don't need to be justified. You don't need to justify your choice of where to eat lunch, or what birthday card to send, or which shampoo to use. But physicians often do things that do need justification, such as sticking people with needles. In the normal run of things, sticking people with needles is considered immoral. But there are many medical situations in which physicians are justified in—and even praised for—sticking people with needles. The reason for this is that when physicians stick people with needles, they prevent more serious harms from befalling those people, and the physicians normally have their permission.

Notice, however, that neither one of these reasons by itself—having permission or preventing harm—is usually sufficient justification for sticking people with needles. You normally need both. That is, even if getting a flu shot is a good way to avoid more serious harm, it's immoral to go around inoculating people who don't want inoculations. But neither does having people's permission to stick them with a needle make doing so okay, all by itself. We don't think very well of someone who is willing to stick people with needles (or remove bodily organs) for no other reason than that the person gave her permission to do so.

Despite the fact that being unprepared for an emergency can provide people with an excuse for suboptimal behavior, the fact that the situation is an emergency rarely excuses the actions of trained emergency personnel. This is because, as noted earlier, the emergencies that emergency personnel are dealing with are rarely unexpected in the relevant sense. That is, emergency personnel have been trained to deal with such situations. Moreover, they have a moral (as well as professional) obligation to be prepared for any sort of emergency they have reason to believe they will be called upon to deal with. So, unless the emergency is quite uncommon, and quite unlike others with which the experienced physician should be familiar—for instance, a case of Ebola virus in a small town in Wyoming—the mere fact that a senior physician is unprepared would itself be a moral failing. But to say that the behavior of experienced emergency personnel is rarely excused because they are dealing with emergencies is not to say that this fact does not often justify what they do. That is, actions of a type that are usually considered immoral may be justified in emergencies, because in emergencies the circumstances are not usual, and the ways in which they are unusual may be morally relevant.

So, there are many medical situations in which it is acceptable (or even good) to do things that would normally be considered immoral. In these situations, health care workers are not excused from standard morality. Instead, standard morality justifies their actions. And there are facts about emergencies that justify actions that would not be justified in non-emergencies. Nonetheless, this does not mean that different moral principles apply in emergencies.

Let us consider a particular principle. One fundamental moral principle of contemporary health care is: Do not treat a patient without first receiving fully informed consent either from that patient or from his proxy. That is, full respect for autonomy demands that physicians (and other health care workers) keep their hands off patients unless those patients or their proxies have given the physicians explicit permission to touch or treat them. Obviously, this is not a principle that is uniformly adhered to in the ED. Nor is it one that the general public would want emergency health care workers to follow. Patients needing immediate medical attention too often arrive at the ED unconscious or incoherent, and taking the time to find a legally designated proxy would too often make effective medical treatment impossible. So, this might look like a principle that applies in standard health care settings, but not in health care emergencies.

However, I don't think that this is a principle applied even in standard health care settings. Notice that no one accepts such a principle—keep your hands off people unless they give you explicit permission to touch them—in non-medical settings and emergencies. Keeping your hands off people unless you have their explicit permission would require, for instance, that lifeguards get permission from drowning people before dragging them to safety, or that firemen get permission from unconscious or frantic people before carrying them out of burning buildings. Clearly, if there is a general moral principle that requires us to respect autonomy by keeping our hands off people unless they give us permission to do otherwise, no one believes that it applies in these emergencies. But my main point here is not simply that no one would endorse this as a good moral principle in such situations. My main point is that no one believes that lifeguards and firemen are typically impinging on the autonomy of those they rescue.

This suggests that there might be something mistaken about thinking that treating an unconscious or incoherent person in an emergency situation normally threatens that person's freedom or autonomy. It is true that an emergency physician should not treat a patient unless she has good reason to believe that the patient wants to be treated. When the patient is conscious and coherent, the best way of determining what he wants is to ask him. But it is possible to have good reason to believe that a patient wants (or would want) to be treated even though he is incapable of expressing that preference. When it comes to most emergency health care decisions, there is a great deal of agreement among people that they would want to be treated. In many actual instances, this gives emergency health care workers very good reason to believe that a particular patient wants to be treated. For instance, one good reason for believing that the unconscious victim of an automobile accident would want her broken arm set is that just about anyone would want his or her arm set in similar circumstances. Thus, the ED staff are justified in setting this patient's arm, in testing for internal injuries, etc., not simply because this is the best way to minimize the harm she will suffer, but also because they have excellent reason for believing that they would have her explicit permission, if she were capable of giving it.

I previously discussed a specific way in which emergencies are sometimes said to be different from non-emergencies. And I have written as if very general principles (such as respecting patient freedom) must be applied case by case in emergencies and non-emergencies alike. Even in the case of the unconscious automobile accident victim, I argued that there was good reason to believe that she would give consent to treatment, in this very case, if she could.

But this focus on individual cases is somewhat misleading. When we talk about medical ethics, in large part we are talking about how to design good moral policies for health care. (What measures must be taken to preserve patient confidentiality, and when are violations of confidentiality required? How should physicians deal with situations in which family members insist on continuing futile care? Etc.) For the most part, writings on medical ethics do not evaluate individual actions, but policies. This having been said, it is clearly important to have policies that apply specifically to emergency situations. Nonetheless, I want to stress that what makes these good moral policies is that they accord with the same moral rules that govern good moral policies for medical practice in general. That is, if a policy designed for emergencies is to be justified, it must be justified by reference to the same moral principles as any other hospital policy.

It is because of the moral importance of such policies that it can even be permissible to override a conscious patient's explicit rejection of emergency treatment. For the most part, any competent person wants to be permitted to make his own decisions regarding his own health care. That is, most people do not want to be at the mercy of what someone else thinks is good for them. But competent people also recognize the need to guard against certain sorts of situations in which they might make bad decisions. So, for instance, most people would not want to have the last word about their emergency care while they are in shock, or under the influence of drugs or alcohol. Similarly, they do not want emergency physicians to be required to act on choices that they as patients might make when they don't have time to hear all the relevant information. So most of us, as people who might at some time need emergency care, prefer ED policies that allow physicians to treat us even when we refuse, if the situation is an emergency and the physician has any question about our competency to refuse. But this does not mean that we would advocate policies allowing her to treat us when she knows that we are competently refusing.

Notice how important it is that emergencies involve time pressure. When there is no time pressure, most of us would not want there to be policies that would allow physicians to make decisions for us. That is not to say that patients want a policy forbidding them from deferring to a physician's suggestion. But that is still a policy in which the patient has the final word. That is because when there is no time pressure, the physician can wait for us to make our own decision, or can find appropriate legal proxies. For instance, if a physician has an appointment to discuss concerns about possible prostate problems, and the patient shows up drunk, it is not a good idea to act on that patient's stated choices. But neither should the physician make the choice for him. In this case, however, this is not a problem. The physician can wait for the patient to sober up, or reschedule for another time.

Obviously, there are characteristics of medical emergencies that make them relevantly different from other medical situations. Only in emergencies do health care workers have a severely limited amount of time in which to make decisions that are likely to significantly affect how much harm a patient suffers. This is important, because it means, for instance, that policies regarding emergencies must allow for decisions to be made quickly. Policies that take a lot of time to follow have different consequences in emergencies than they do in other health care settings, and those consequences could be disastrous. So, for instance, in emergencies health care workers must be allowed to act with less information than would be required in non-emergency situations—less information about what a particular patient wants, but also about her medical history, and even about her current ailment. Without such policies, many more people would die or suffer additional physical harm: something both health care workers and patients certainly want to avoid.

I hope I have shown that many principles, including respect for patient freedom, are just as important in emergencies as they are elsewhere. Because of the unique characteristics of emergencies, respecting these principles may take different forms than in non-emergencies, but they are no less important. Nor does the fact that a situation is an emergency provide health care professionals with an excuse for taking the situation less seriously.

Creating policies is really a way of planning. It is a way of thinking ahead of time about what one will do in a variety of different situations. And thinking ahead of time about predictable decisions is what ensures that when the ED staff is confronted with an emergency it is capable of dealing with it as responsibly as possible—both medically and ethically. Even relatively mundane policies, for instance, those that govern admitting patients or storing supplies, contribute to—or should contribute to—providing for the welfare of patients. If there were no policies concerning these things, new decisions would have to be made constantly, and this would certainly waste a great deal of precious time. Similarly, there must be policies regarding who has which responsibilities, and what, precisely, those responsibilities are. Again, making these decisions on an *ad hoc* basis would take time precisely when that time is needed most, and this is why policies designed specifically for the ED are necessary.

Conclusion

It is certainly true that emergencies are different from other medical situations, and this fact morally requires that there be policies designed especially for emergency situations. But the unique nature of emergencies does not mean that those who provide emergency medical care are excused from standard morality, or that a different set of basic moral principles apply. It is also important to recognize that the moral requirement for designing policies for emergencies is broad, and does not apply merely to decisions that obviously fall under the purview of medical ethics, such as those having to do with informed consent or decisions regarding the futility of treatment. It applies to any aspect of what happens in emergency situations that has the potential for affecting the welfare of patients.

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What Part of “No” Don’t You Understand?

Patient Refusal of Recommended Treatment in the Emergency Department

Arthur R. Derse, M.D., J.D.

Abstract

Patient refusal of indicated medical treatment, especially when the treatment would be life sustaining, presents all physicians, especially emergency physicians, with the responsibility of determining whether the patient has the capacity to refuse treatment, and whether the patient’s refusal is informed. These two crucial questions present a number of dilemmas for physicians who may have no prior relationship with that particular patient. The ethical and legal principles for determining decision-making capacity and assuring that refusal is informed are described, and an algorithm for responding to patient refusals is presented.

Key Words: Informed consent, informed refusal, life-sustaining medical treatment, decision-making capacity, emergency treatment, emergency privilege.

One of the most vexing problems for emergency physicians occurs when a patient comes to the emergency department but refuses treatment that, in the emergency physician’s opinion, is either indicated or, in some cases, necessary to treat life-or-limb-threatening emergencies. The immediate problem is whether or not to honor that refusal. Such decisions, which have to be made in less than ideal circumstances, can have drastic implications for the health or life of the patient. In some cases, drastic measures to coerce the patient to be treated against his or her expressed refusal are necessary (1). These dilemmas are fraught with ethical and legal implications (2).

The emergency department environment is unique. It is open to all who have emergent or urgent medical problems, and it is required by federal law to evaluate the patient and, if the patient has an emergent medical condition, to treat the emergency or to stabilize and transfer the patient to a facility that can definitively treat the patient (3). The emergency department is also the place where patients who are indigent or uninsured may seek treatment for medical conditions. Such patients may have either avoided prior medical treatment or have been turned away from outpatient treatment for financial reasons. Patients often seek care at the closest medical facility, and the emergency physician is usually not chosen by the patient. Typically, there has been no prior doctor-patient relationship and thus no previous opportunities to build trust. The patient is frequently brought to the emergency department involuntarily by ambulance, either at the insistence of others, such as family members or friends, or in other cases, at the behest of the police at a crime scene. The patient has often experienced a sudden change in health status and may be in pain, be anxious, or have an altered mental status. Decisions must be made quickly, often with incomplete information, since the patient’s medical records may be unavailable (4). The emergency environment may also be characterized by a lack of patient privacy. Emergency departments are often constructed as arenas, with bays of beds separated by curtains to allow the maximum visual-

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Director of Medical and Legal Affairs, and Associate Director, Center for the Study of Bioethics, Clinical Professor of Bioethics and Emergency Medicine, Medical College of Wisconsin, Milwaukee, WI.

Address all correspondence to Arthur R. Derse, M.D., J.D., Center for the Study of Bioethics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509.

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ization of many patients. The corresponding openness results in interactions between physician and patient being visible and audible by other staff and, at times, other patients (5, 6).

It is in this less than ideal environment that emergency physicians have to obtain consent to treat patients and to evaluate patients who refuse recommended medical treatment, including life-sustaining medical treatment. The ethical and legal requirement of informed consent has long been a mainstay of the relationship between physician and patient. Consent is required for procedures, testing, treatment and research, even if the procedure is essential for the patient (7). Informed consent in most circumstances need not be accompanied by written documentation. Verbal informed consent may be adequate, although these patients will be asked to sign a general consent for treatment, and the law or hospital policy may require that some tests and procedures be accompanied by the informed consent and signature of the patient or patient's representative.

The elements of information that must be disclosed include the risks, benefits, and alternatives, including the anticipated results of no treatment (8). There are two legal standards for disclosure of information. The traditional standard mandates that the physician disclose to the patient what the average prudent physician would disclose to the patient. This standard was set by the medical profession and is known as the "professional standard." A majority of the states now require that the information that must be disclosed conform to a standard set by what the "objective patient" would find material to the decision of whether or not to undergo the procedure. This is known as the "objective patient standard" (9). Under the professional standard, expert witness testimony is required to establish whether a physician met the standard or not. Under the objective patient standard, the jury, without expert testimony, determines whether or not the physician met the standard. The professional standard might appear to be a higher hurdle for a plaintiff-patient, since physicians might be less likely than a jury, in retrospect, to find a particular piece of information necessary to disclose. However, the increased willingness of physicians to testify as experts for the plaintiff has led to less of a practical difference between the two standards.

Informed consent, however, is not required under all circumstances. There are two well-recognized ethical and legal exceptions. The first is the emergency exception to informed consent, known in the law as the "emergency privilege." Patients may be treated without their informed consent when these criteria are fulfilled: The patient lacks decision-making capacity (e.g., is unconscious); no one is available who is legally authorized to act for the patient. Time is of the essence in that there is a serious risk of bodily injury or death. Given the serious risk, it is assumed that a reasonable person would consent if he or she were able to (10).

The emergency privilege allows emergency physicians to act in emergencies to treat patients without consent in many clinical situations, for example, when comatose patients are brought in critical condition to the emergency department. Emergency physicians are usually aware that this exception gives them permission to treat patients without consent but often do not recognize how circumscribed it is. For example, the emergency privilege does not allow emergency physicians to treat competent patients with emergent conditions who refuse treatment, or incompetent patients who have a legal representative authorized to accept or refuse recommended medical treatment.

The second exception to informed consent is known as the "therapeutic privilege," which allows treatment without full disclosure to the patient of the medical circumstances necessitating treatment. This exception is allowed only when full disclosure of the patient's medical condition would have such an adverse effect on the patient that it might render him or her unable to make a medical decision or might cause psychological or even physical injury (for example, extreme distress, depression, thoughts of suicide). In such cases, reasonable discretion must be used in the manner and extent of the disclosure, and full disclosure must be made at the first opportunity, when the patient would no longer be so distressed by the information that he or she could not make a medical decision. This exception, although it has legal precedent, should rarely be invoked, since its routine use would undermine the autonomy of patients (11).

It is an obvious corollary that since consent is needed to treat patients even when the treatment is medically necessary, patients also have the concomitant right to refuse treatment. This right to refuse medical treatment extends to the right to refuse even life-sustaining medical treatment. The right of a guardian to refuse treatment for a patient was first recognized by a state court in the case of Karen Quinlan (12), and subsequently recognized as a federal 14th Amendment liberty interest in the case of Nancy Cruzan (13). Patients with a terminal condition have the right to refuse medical treatment, but patients need not have a terminal condition to refuse life-sustaining medical treatment (14). Elizabeth Bouvia, a woman with cerebral palsy, was recognized by a California appellate court to have the right to refuse nutrition and hydration (15), and state courts have recognized the right of competent Jehovah's Witness patients to refuse life-sustaining medical treatment in the form of blood transfusions, even if that refusal would result in the patient's death (16). One of the most vexing ethical conundrums for emergency physicians occurs when a patient who does not have a terminal illness refuses life-saving treatment for what appears to be a very treatable—and reversible—condition. The emergency physician's predisposition by training, and often by temperament, is to intervene to preserve life. It is often counterintuitive to emergency physicians that patients should have the right to refuse well-intentioned life-sustaining treatment. In fact, emergency physicians often express the opinion that a good medical outcome should trump a patient's refusal. Emergency physicians often cite a legal canard that "No one has ever been successfully sued for erring on the side of preserving life," even in the face of patient refusal. If this was ever true, it is no longer so. Life-saving treatment against a competent patient's refusal may result in a suit for battery, medical negligence, and lack of informed consent (17).

A patient's refusal of treatment does not end the physician's responsibilities. Patients who refuse medical treatment have the right to be informed of the consequences of their refusal (18). This can be difficult to do in the emergency department, since patients who refuse medical treatment are often unwilling to engage in further conversation about their refusal and may feel that any further information is merely being used to pressure them into acceding to the physician's recommendation. But even informing the patient about the consequences of refusal does not end the physician's duties.

Since patients who have the capacity to make medical decisions have the right to refuse treatment, even life-sustaining medical treatment, and the consequences of such refusal can be grave, the determination of whether the patient is able to make decisions about his or her medical care is of crucial importance (19). Though the term "competence" is used in common parlance to refer to a person's ability to make important personal or financial decisions, and in legal contexts to refer to the legally recognized ability of an individual to make decisions about his or her person or property, it is recognized that there are circumstances in which patients who have not been found by a court to be incompetent are nonetheless unable to make medical decisions (e.g., the competent person who is temporarily unconscious due to an anesthetic). Conversely, there are persons who may be legally determined to be incompetent but may nonetheless be able to express their wishes to a physician concerning medical procedures (20). Since the ability to make decisions about medical care may differ from competency according to legal determinations, "medical decision-making capacity" has become a preferred term when considering the ability of a patient to make a specific medical decision at a specific time.

Medical-decision-making capacity is present when the patient is able to understand information about the medical condition and its consequences, to reason and deliberate about the various choices, to make a choice consistent with his or her values and goals, to communicate this choice to the physician, and to maintain this choice consistently over time. Any break in this chain of elements constitutes a lack of decision-making capacity (21).

Thus, a patient lacks decision-making capacity if he or she cannot understand the information needed to make a medical decision, reason about the information in light of personal values and goals, or reach a decision and communicate it clearly and consistently.

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research further delineated the nature of decision-making capacity, recognizing that it is dependent upon the individual abilities of the patient, the requirements of the task at hand, and the consequences of the decision. When the consequences of the decision are substantial, there is a greater need for certainty of the patient's decision-making capacity (22). Thus, a physician who encounters a request from a patient to forgo a life-saving intervention has a duty to determine whether the patient has the capacity to refuse such treatment.

Decision-making capacity is not necessarily established by a patient merely expressing a preference, by the content of the decision conforming to a socially determined "objectively correct" standard, or even by its concurrence with the physician's recommendation. There are some patients who are obviously incapable of making medical decisions: infants, young children, patients who are comatose or severely mentally handicapped. Whether or not other patients have decision-making capacity may not be so straightforward.

An assessment of decision-making capacity must assess the patient's ability to (a) understand, including comprehending information and appreciating consequences; (b) evaluate, comparing risks and benefits, and to make a rational and consistent choice; and (c) communicate that choice. The patient's ability to weigh choices against personal values and consistency of choice must be tempered by the fact that some patients may change their values and their decisions over time, and others may make decisions that take into account their family relationships and religious, philosophical, cultural and societal values.

A traditional test used to determine a patient's mental status is the Mini-Mental Status Exam (MMSE), which tests orientation, memory, attention, and reasoning ability (23). But this test of mental status may not address critical issues of decision-making capacity, namely the ability to weigh personal values and to make decisions on the basis of those values (24). The ability to assess decision-making capacity should be a skill that is a routine part of emergency medical practice, although more complex evaluations may require consultation with a mental health professional (25). Nonetheless, many of these evaluations must be done under urgent or emergent circumstances. Physicians routinely make these determinations on an informal basis during their conversation with the patient.

It has been observed that questions of patient decision-making capacity typically arise when a patient chooses a course, often a refusal of treatment, that goes against the course that the treating physician finds most reasonable (26). While it is true that physicians generally do not question the decision-making capacity of patients who follow their recommendations, for emergency physicians, patient refusal of life-sustaining medical treatment may have fatal consequences. The determination of decision-making capacity is therefore critical. Importantly, it may not follow that if one has the capacity to consent to treatment, one must also have the capacity to refuse treatment. The reason for this inequality is that concern for the patient's well-being must be balanced against respect for the patient's self-determination. If the likely consequences to the patient's well-being are very harmful (e.g., disability or death) if the patient refuses, and very beneficial if the patient accepts treatment, it has been argued that the patient needs a higher level of decision-making capacity to make the negative decision. And if the treatment would be beneficial to the patient, the level of decision-making capacity to accept it need not be as high (27).

Patients who are mentally ill, drug dependent or developmentally disabled, or who manifest behavior or statements that evidence a substantial probability of harming oneself or others may be emergently detained for treatment under statutory authority. And patients whose judgment is impaired and who are at risk of physical impairment or injury due to that impairment (e.g., patients with advanced dementia) may also be detained and treated under statutory authority pending guardianship.

More challenging are those patients who do not appear to be mentally ill, impaired by drugs or alcohol, or by dementia, and yet express a seemingly irrational choice by refusing needed life-saving treatment. These patients may express a bias toward the present and near future over longer-term goals; for example, a patient may wish to put off treatment of a heart attack in order to go home to take care of a pet. They may also demonstrate an unrealistic attitude toward risk, weighing the small risks of anesthesia for surgery for appendicitis as greater than the actually extremely higher risks of a ruptured appendix. Another type of irrational choice occurs when patients' fear of pain or the medical experience outweighs the benefits of treatment, for example, in the case of a patient who is undergoing a severe and possibly fatal allergic reaction but refuses treatment because of a fear of needles. Finally, there is a seemingly irrational choice involved when the patient views what will be lost as much greater than what will be gained, e.g., the young patient who refuses the needed appendectomy because a scar would interfere with a future career in modeling (28). These patients present serious dilemmas for emergency physicians who wish to balance their patients' right to be free from unwanted medical care against their need for emergency intervention. Situations such as these may call for the assistance and expertise of mental health professionals.

Common pitfalls in determining decision-making capacity have been identified (29) and grouped into a list of ten so-called "myths" about decision-making capacity (30):

1. Decision-making capacity and legal competency are equivalent. This myth is rebutted by the recognition that on the contrary, as discussed above, they are different categories, though they may often overlap.
2. A patient who refuses to follow medical advice obviously does not have decision-making capacity. On the contrary, patients who possess decision-making capacity have the ethical and legal right to refuse even life-sustaining medical treatment.
3. A patient who follows medical advice obviously possesses decision-making capacity. Though this may often be true, patients who lack decision-making capacity, such as patients with severe dementia, may be very compliant patients.
4. Decision-making capacity is an "all-or-nothing" ability. That is, a patient who cannot make

one type of medical decision cannot make any medical decisions. On the contrary, decision-making capacity is dependent upon the decision to be made. A patient who is unable to make a decision about a life-threatening problem might be able to make a decision regarding his or her preference as to how a medication should be administered.

5. A patient who has some cognitive impairment is therefore unable to make any medical decisions. Both legal precedent and geriatric practice contradict this myth (31). Patients may have varying degrees of cognitive impairment that may or may not affect decision-making capacity.
6. Once a patient is incapacitated, the incapacity is permanent. Not true. For example, a patient incapacitated by intoxication will probably recover decision-making capacity, and even patients who have dementia may have fluctuating periods when they have the ability to make some medical decisions (32).
7. Patients who lack information to make a decision therefore lack the capacity to make medical decisions. On the contrary, the ability to understand information is central to decision-making capacity, but a lack of information does not imply a lack of ability to make decisions.
8. The fact that a patient has a psychiatric diagnosis means that the patient is not able to make medical decisions. Not so. A patient who has a diagnosis such as schizophrenia may well have impaired decision-making capacity for certain periods of time, but may be able to make medical decisions during others despite the underlying psychiatric condition.
9. Patients who are involuntarily committed for mental health treatment are not able to make medical decisions. On the contrary, many states' laws allow patients who are involuntarily committed to make some medical decisions and even to refuse psychotropic medications unless they are an imminent danger to themselves or others.
10. Only mental health experts may assess decision-making capacity. On the contrary, as noted above, all physicians, especially emergency physicians, should have the ability to assess decision-making capacity. Mental health expertise may be necessary in more complex cases.

Once a patient has been determined to lack decision-making capacity, emergency physicians are charged with making decisions in the best interest of the patient or according to the patient's preferences, if the patient has expressed treatment preferences before becoming incapacitated, for instance, in an advance directive. The emergency physician should also seek to identify a decision maker for the patient, such as a guardian, health care agent, or other surrogate such as a spouse, family member, or close friend.

Even with these guidelines, several additional problems face emergency physicians when encountering a treatment refusal. What words or actions constitute a refusal by a patient with decision-making capacity? How consistent must the patient's refusal be? What level of certainty that the patient is able to make the decision to refuse life-sustaining medical treatment should be required before a patient may choose a course that risks almost certain death? And to what degree may liberty be restricted until a determination of decision-making capacity is made?

The following algorithm may help in considering how to address patients who refuse medically indicated treatment.

Algorithm for Patient Refusal of Medically Indicated Treatment

1. Does this patient have decision-making capacity?
- If yes, the patient may refuse even life-sustaining medical treatment

    Be sure the patient understands the risks and consequences of refusal and accepts those risks, utilizing careful documentation and a witness to the discussion when necessary. If the decision entails life-threatening consequences, consider the role of the patient's family or friends in helping the patient weigh the decision carefully and asking the patient's permission to involve them in the discussion.

- If no:
    2. Is the non-decisional patient under legal protection such as emergency mental health detention or court order?
        - If yes, treat within the constraints of the legal restrictions
        - If no:

    3. Does the non-decisional patient have a legally authorized decision maker, a document indicating a power of attorney for health care, or a living will that expresses the patient's preference?
        - If yes, is the decision maker available?
            - If yes, consult the decision maker

        - If no, and this is not an emergency, seek the decision maker
    - If there is no legally authorized decision maker or document and this not an emergency, seek a new legally authorized decision maker such as a guardian

  4. Is this a bona fide emergency (i.e., a life- or limb-threatening condition)?
     - If no, seek a legal decision maker
     - If yes, (i.e., there is a life or limb threat AND time is of the essence AND no legally authorized decision maker is available AND a reasonable person would consent):
         - Act in the best interest of the patient and concurrently seek a legally authorized decision maker

- If the physician is unsure whether the patient has decision-making capacity:
  5. Will the patient allow a determination of decision-making capacity?
     - If yes, determine decision-making capacity by evaluating the patient's ability to understand information, evaluate the information and communicate a decision
     - If no, weigh the need to ascertain the patient's decision-making capacity against the harm of allowing the patient to refuse without a determination of capacity.
         - If there is a need to determine whether the patient is decisional, use the least restrictive and least invasive means of determination, emphasizing the need to the patient to determine decision-making capacity and concern for the patient's best interest. If necessary and if time allows, seek professional mental health expertise.

Patient refusals of indicated medical treatment, especially life-sustaining medical treatment, present emergency physicians with the responsibility of determining whether the patient has the decision-making capacity to refuse treatment and whether the patient's refusal is informed. This responsibility must be balanced against the patient's ethical and legal right to refuse life-sustaining medical treatment. The necessity of determining decision-making capacity and providing information to the patient about the consequences of refusal is central to making certain that patient autonomy is respected and that patients who cannot make autonomous decisions are protected from harm. When a patient inexplicably refuses indicated medical treatment, especially life-sustaining medical treatment, the discussion—and the need for careful consideration by the emergency physician of the patient's decision-making capacity—has not ended, but has just begun.

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Mandatory Reporting of Domestic Violence:

The Law, Friend or Foe?

Laura G. Iavicoli, M.D.

Abstract

Should physicians be mandated to report domestic violence involving a competent adult patient regardless of whether or not he or she consents to the report? This is a complex ethical and moral issue; in some states such as California, Colorado, Kentucky, New Hampshire, Rhode Island and New Mexico it has become a legal one as well. The Federal health privacy regulation instituted in the Health Insurance Portability and Accountability Act of 1996 (HIPAA) addresses issues of privacy protection for survivors of domestic violence, but it does not preempt those state laws that are less (or more) protective of patient privacy. In the above states, physicians and/or health care providers are mandated to report acts of domestic violence to an agency, under their own circumstances, regardless of whether the physician or health care worker believes that reporting the violence is in the patient's best interest or not. But is mandatory reporting truly "good" or "bad" for the patient, the physician or society as a whole? This article explores the laws and the evidence (including evidence-based research) surrounding the issue of mandatory reporting of domestic violence when it pertains to a competent adult.

Key Words: Domestic violence, mandatory reporting, domestic assault, law, adult.

Case Presentation

A FORTY-ONE-YEAR-OLD FEMALE presents to the emergency department with a chief complaint of abdominal pain and vaginal bleeding. At triage she responded "yes" to the domestic violence screening questions of "Domestic violence ever?", "In danger tonight?", "Afraid of partner?", "Social worker referral accepted?" and added that the last assault was two weeks ago. The perpetrator is her husband.

Upon further questioning the patient states that she was sexually and physically abused by her husband last Saturday. She says he kicked her until her leg was black and blue, and he assaulted her intravaginally with his fist. Patient reports that her partner has threatened to kill her if she reports him. She believes he would do this, as he has tried to choke her in the past.

She states that she has never reported previous incidents of domestic violence, although she has received medical treatment in the past. She is terrified to file a police report or orders of protection. She refused to allow photos of the injuries. She alleges that the violence has been escalating since her husband recently became involved with another woman, and that her husband and his girlfriend are abusing drugs and alcohol. She lives with her partner in a room in someone's apartment and she has no relatives who can take her in. At this time, she says it is safe for her to return home, because her husband promised her pastor that he would leave her alone. However, the patient also states that her husband is a big man and that she and her relatives are fearful of him.

On physical examination, the patient was found to have multiple upper and lower extremity bruises in various stages of healing, moderate blood in the vaginal vault, and a 2 cm laceration of the lateral vaginal wall. The laceration was noted and repaired by Gynecology in the Emergency De-

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The Mount Sinai School of Medicine, New York, NY, and Elmhurst Hospital Center, Elmhurst, NY.

Assistant Professor of Emergency Medicine, Department of Emergency Medicine, The Mount Sinai School of Medicine, Box 1620, One East 100th Street, New York, NY 10029, and Director, Division of Emergency Management, Elmhurst Hospital Center, 79-01 Broadway, B1-14, Elmhurst, NY 11373.

Address all correspondence to Laura G. Iavicoli, M.D., 150 East 2nd Street, Apt. 3A, New York, NY 10009; e-mail: lauramd97@hotmail.com

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partment. The patient was also treated for gonorrhea (GC) and chlamydia because she reported a foul, yellow vaginal discharge for 6 days, and she was counseled to use a condom with her husband if possible. A rapid plasma reagin (RPR) for syphilis was sent. The patient was found to have no other injuries and was scheduled to follow up with the Infectious Disease Clinic for HIV testing as well as the Women's Health Clinic in 1–2 days. She was counseled by the social worker, sexual assault coordinator and sexual assault and violence intervention (SAVI) advocate while in the Emergency Department. Finally, she was discharged and returned home.

The emergency department is often the first place that the battered turn to in times of distress. And the numbers of those affected are startlingly significant. Domestic violence affects 2–6 million adults per year, with 1 million adults assaulted per year. One-half of those assaults result in injury. Of these, 43,000 injuries are gunshot wounds, stabbings, broken bones, internal injuries and loss of consciousness. Another 53,000 injuries are intimate partner rape or sexual assault; 390,000 injuries are bruises, cuts, and swelling; and in 1996 some 1,800 murders were committed by an intimate partner. In all of these cases, a third of the survivors seek medical care in an emergency department or clinic (1).

The management of a patient who presents with injuries due to domestic violence raises a number of legal and ethical issues for the physician. What is a physician's legal responsibility in terms of reporting the act of violence to the appropriate law enforcement agency? Would it be in the patient's best interest for a mandatory reporting law of domestic violence for physicians to be in place? What are the laws currently in place regarding domestic violence and mandatory reporting for physicians?

When discussing issues of medical privacy regulations, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a good place to start. It mandates a federal health privacy regulation that addresses, among other things, the issue of privacy protections for survivors of domestic violence. HIPAA required that the secretary of the Department of Health and Human Services (HHS) issue health privacy regulations if Congress failed to do so by 1999. Congress failed to act by the deadline, so the secretary proposed regulations in November 1999 and published them in the Federal Register in December 2000. They were effective as of April 2001. The regulations are available at http:/aspe.hhs.gov/admnsimp/. Most health care entities that fall under this legislation must comply within 2 years of the effective date.

The caveat of HIPAA is that the health privacy regulations regarding consent and disclosure of health care information for domestic violence victims do not preempt state laws that are more or less protective of patient privacy. For instance, in cases of child abuse and neglect, no prior consent is needed to disclose this information for law enforcement purposes, jury and administrative purposes. All 50 states have mandatory reporting laws for child abuse and neglect. In addition, there are several circumstances in which entities may disclose protected health information without written consent from a competent adult. These circumstances include: (a) if the individual agrees, (b) if disclosure is required by law (mandatory reporting), or (c) if the disclosure is authorized by statute or regulation (2).

Thus far, six states have instituted mandatory reporting laws for domestic violence. These are summarized in the Table (3). There is currently no law in New York State that requires physicians or other health care workers to report domestic violence assault. The physician in the above case was therefore prohibited from reporting the incident described, even if the physician believed the woman to be in imminent danger. What is the right thing to do? Does reporting domestic abuse enhance patient safety or increase the danger?

Those who support mandatory reporting believe that it facilitates prosecution of batterers. This in turn sends a clear message to society that domestic violence is a crime and will not be tolerated. Many feel that the strongest deterrent to continued violence is incarceration or court-ordered counseling. In mandatory reporting states, the perpetrator can be convicted without the cooperation or participation of the victim. Mandatory reporting also encourages clinicians to identify domestic violence and improves data collection (4). In addition, advocates feel that documentation and treatment is improved by these laws, professional training is increased, perpetrators are held responsible for their actions, and patient safety is enhanced, since without the report the violence only escalates (1). In addition, many women state that the onus of reporting is removed from them and feel a sense of relief that it is put in the hands of someone else (5).

The literature is strewn with anecdotal evidence for and against mandatory reporting. Two cases in support of mandatory reporting follow:

1. A female patient seen by a physician was repeatedly strangled by her spouse and feared for her life. The patient was reluctant to seek help, and when she did, the physician reported the domestic violence

TABLE

State	Mandated Reporter	Receiving Agency	Basis
California	health care workers	police	"reasonable suspicion" of domestic violence
Colorado	physicians	police	"an injury caused by a criminal act (e.g., a weapon), including domestic violence"
Kentucky	health care worker	Cabinet for Human Resources, which then notifies police, investigates, drafts a report of findings and recommendations	"suspected abuse"
New Hampshire	health care worker	police	"an injury caused by a criminal act (e.g., a weapon), including domestic violence, unless the victim is older than 18 years old and objects"
Rhode Island	health care worker	police	"wounds from weapons and domestic violence for 5 years for data collection"
New Mexico	health care worker	police	"incidents of domestic violence"

to the police, as the physician was mandated to do by law. The reporting physician states, "Later I saw her again, and she said to me, 'There is not a day that goes by that I am not grateful for that report you made' "(6).

2. A physician treated a domestic violence victim, but despite police and social service efforts the victim was shot by her batterer the next morning. The physician states, "I recognized the signs, I was able to get her to tell her story. I know I did everything, along with police and the advocate, to try to help her. I can't imagine how I would feel if I had done nothing" (1).

There is also evidence-based literature supporting and opposing mandatory reporting. In support is an article published in *JAMA* in 2001, which found that a majority of recently abused female patients who presented to the emergency department supported mandatory reporting (4). According to Houry et al., 62% of emergency department patients felt that mandatory reporting laws did not make a difference in seeking health care, 27% were more likely to seek emergency department care and 12% were less likely to seek care due to the legislation (5). Both Malecha et al. and Sachs et al. have concluded that laws do not deter patients from seeking care and that survivors don't believe laws put them at greater risk for future violence (3, 7).

Those opposing mandatory reporting feel that it will increase violence by perpetrators, diminish patient autonomy and compromise physician-patient confidentiality (4). This group also feels that mandatory reporting places patients at risk for retaliation and possibly deters patients from seeking medical care for their injuries. It is argued that the quality of medical care may suffer, because physicians may overlook injuries or they may not inquire about injuries if they are opposed to the legislation. Finally, the doctrine of nonmaleficence is violated (1). A physician is sworn to do no harm first and foremost, but in some cases, for reasons stated above, mandatory reporting may force the physician to perform an act that is thought to be harmful to the patient in that particular patient's circumstances.

Anecdotal reasons for opposing mandatory reporting can be as vivid as anecdotal reasons for supporting it.

1. Joanna was treated in the emergency department for facial injuries that were inflicted by her intimate partner. The physician did what was mandated and filed a re-

port. Joanna's husband was arrested and Joanna returned home thinking it was safe, since the perpetrator was behind bars. However, unknown to her, her partner had been released and was waiting for her at home. He proceeded to inflict even more severe injuries than the first time.

2. Another case involved a women named Donna, who was injured by her boyfriend. She went to the hospital to seek help for her injuries but was afraid to enter because of the mandatory reporting laws. Instead she spent the night in her car in the hospital parking lot and did not receive the medical care she needed (1).

There is also literature opposing mandatory reporting. Gielen et al. found that two thirds of the women they surveyed believed that mandatory reporting decreased the likelihood of disclosing abuse. The abused women in the study felt that their autonomy was lost and they "resented" the physician. The abused women also felt that fear of the perpetrator was a barrier to disclosure (8). Rodriguez et al. reported that abused women felt that mandatory reporting jeopardizes safety of the survivor, deters the survivor from seeking medical care and compromises confidentiality and autonomy. In addition, the women feared increased violence and family separation, and had a general mistrust of the police (9). Finally, Feldhaus et al. published a study done in Colorado, a mandatory reporting state, and found that sexual assault victims don't want the crime reported, due to embarrassment, fear of the assailant and fear of others finding out (10).

There is much to be done before the issue of mandatory reporting can be resolved. First and foremost, more research is needed on the impact of the existing laws on survivors of abuse. Risks and benefits of mandatory reporting need to be studied and hypotheses need to be tested in large-scale, multi-center trials. The issue of women's safety must be specifically addressed during these trials. The National Academy of Sciences committee for the Institute of Medicine proposed that states with domestic violence laws be tested and evaluated by research before enacting more mandatory reporting laws. The American Medical Association (AMA) proposed that mandatory reporting statutes that are in place should include patient identity protection and a clause for competent adults to opt out of reporting. Another suggestion is that reports be made out to public health agencies, which would then evaluate and investigate the report before turning it over to the police. The AMA also recommended that the mandatory reporting statutes have a "sunset clause" built in, so that the legislation would be in place for a limited number of years before it was re-evaluated. Understanding what is best will require well-designed research that involves professionals in the medical, social service and legal fields as well as survivors of abuse and patient advocates (1).

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Adolescents, Informed Consent and Confidentiality:

A Case Study

Reza Keshavarz, M.D., M.P.H.

Abstract

Issues related to informed consent and confidentiality often arise in the emergency care setting. When the patient is an adolescent further complexities are introduced, especially when the desires of the adolescent are different from those of the parent. Understanding when an adolescent can give informed consent and what the limits of confidentiality are will assist medical personnel in providing the most appropriate care. These concepts are elucidated with a specific case.

Key Words: Informed consent, confidentiality, emergencies, adolescents.

In mid-summer, a 14-year-old youth was brought to the pediatric emergency department by his mother, for evaluation for altered mental status. The mother returned from work to find her son acting strangely. She had last seen him the previous evening and there were no problems or complaints at that time. Earlier in the week the child had sustained several mosquito bites. The child was now at times lethargic and at other times agitated. There were two episodes of vomiting. There was no history of fever trauma, medications or known ingestions. The medical history was negative. The social history was significant for a high-achieving honor student who came from a very financially successful household. Physical examination revealed a drowsy and disoriented athletic male. The vital signs were temperature of 37.8° Celsius, heart rate of 107 beats per minute, respiratory rate of 20 per minute and blood pressure of 123/87 mm Hg. The general physical examination was unremarkable. The neurologic examination revealed a disoriented teenager with ataxia, brisk reflexes throughout, reactive pupils and intact cranial nerves II through XII. A bedside glucose test and pulse oximetry were both normal. Given the ongoing epidemic of West Nile virus at the time of presentation, the mother was convinced that the child had contracted the insect-borne disease because of the combination of mosquito bites and altered mental status. The mother was absolutely insistent that a spinal tap (lumbar puncture) be performed immediately, to evaluate for the possibility of West Nile virus.

The patient's pediatrician was also concerned and requested a full and thorough evaluation. An intravenous line was started and routine blood evaluations were ordered. The patient seemed at times to be more lucid, but at other times was again disoriented. When interviewed alone, he denied having West Nile virus, but he agreed to tell the physician why he believed this to be the case, but only if his parents were not told. The physician explained that all information given by the patient would be kept in strict confidence. Because of the assurance of confidentiality, the patient disclosed that he had bought a large amount of dextromethorphan on the Internet and had taken it with his friends after school.

Dextromethorphan ingestion, even in large quantities, generally does not require anything but supportive care. The mother, not knowing about the ingestion of this drug, continued to be insistent that further tests be performed, including a spinal tap.

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Reza Keshavarz, M.D., M.P.H., Department of Emergency Medicine, Box 1149, One East 100th Street, Mount Sinai School of Medicine, New York, NY 10029.

Presented at the Issues in Medical Ethics Conference on "Special Challenges of Emergency Medicine" at the Mount Sinai School of Medicine, New York, NY.

The case brings up a number of issues for consideration by the clinician treating the patient. There is the practical question of what to do with the patient and what if anything to tell the mother. In order for the physician to determine the most appropriate course, thoughtful consideration should be given to a number of questions:

1. Can this fourteen-year-old give informed consent for his own treatment or lack thereof?
2. Is the patient either a mature minor or an emancipated minor?
3. Is it important for the clinician to tell the truth, and if so to whom? The patient? The mother? The patient's pediatrician?
4. Is the information given by the patient to be held in strict confidence?
5. Finally, given the conflicting duties, should the physician:
   a. act in the best interests of the patient?
   b. respect patient autonomy?
   c. tell the truth?
   d. keep patient confidentiality?

Each of these questions will be dealt with individually. In the following discussion, arguments are drawn from both ethics and the law. While similar and interrelated, these two disciplines may lead the physician in divergent directions in specific situations (1).

Can This Fourteen-Year-Old Give Informed Consent for His Own Treatment or Lack Thereof?

While informed consent is a generally accepted doctrine in the treatment of patients in most situations, it is not always possible to adequately explain and discuss the full range of possibilities in an emergency setting. Unconscious patients, those who are severely intoxicated, and those with conditions that are immediately life-threatening are examples of patients for whom proper informed consent is not possible. In the treatment of minors, emergency care is not typically withheld if there is no guardian or parent present to give consent for treatment (2). The definition of "emergency care" may include not only life-threatening illnesses, but also the treatment of pain and interventions that have the potential to prevent disability (3). A minor (defined as less than eighteen years of age in most states) cannot give consent, informed or otherwise, in most medical situations (some of the exceptions are detailed below). However, parental consent is not typically necessary either, at least in the initial evaluation and stabilization of a minor. The Committee on Bioethics of the American Academy of Pediatrics has gone on record as saying that "the doctrine of 'informed' consent has only very limited direct application in pediatrics" (4).

Federal regulations, generally cited as Consolidated Omnibus Budget Reconciliation Act / Emergency Medical Treatment and Active Labor Act (COBRA/EMTALA) regulations, specify that a medical screening examination be performed, including any necessary stabilization, for all patients presenting for emergency care. And this must to be done regardless of all other factors, including the age of the patient and ability to pay for the medical care provided (5). The medical screening examination was performed for the patient under discussion in accordance with these guidelines.

Is the Patient Either a Mature Minor or an Emancipated Minor?

Exceptions to informed consent can be classified under three headings:

1. The treatment of certain specific conditions. Many states allow minors to seek medical care for the treatment of certain conditions, including sexually transmitted disease, pregnancy or drug/alcohol abuse (4, 6).
2. The treatment of "mature minors." Under certain situations, minors can be considered mature and able to consent for treatment without the involvement of a parent or guardian. A few states allow minors, generally at least 14 years of age, who are thought to have adequate maturity and reasoning capability, to consent for their own health in general (3, 5). This consent would generally be adequate for conditions the treatments of which, by their nature, have small degrees of risk (7). And the adolescent must be able to understand the risks and benefits of the various treatment possibilities (8).
3. The treatment of "emancipated minors." These are adolescents who do not live at home and are self-supporting, are married, are pregnant or have a child of their own, are enlisted in the military, or have been declared emancipated by the court (4).

The patient presented in this case would not fulfill the criteria of any of the above exceptions to informed consent. But if he had come in seeking help for his drug problem, he could have received care without the involvement or consent of a parent.

Is It Important for the Clinician to Tell the Truth, and If So to Whom? The Patient? The Mother? The Patient's Pediatrician?

Although today most physicians would regard telling the truth to patients as important, this has not always been the case (9). It was not uncommon in the past for physicians to withhold relevant information about a patient's prognosis, especially if that prognosis was poor. Certain cultures may value and expect the truth from their physicians more than others (10). Historically, paternalism has at times been more important that truth telling and respect for patient autonomy. Presently, telling the truth and involving patients (including children) in their own health care are often considered important principles (11).

In the current case, the physician cannot tell the truth to both the child and the parent. The promise of confidentiality that the provider gave the teenager comes into conflict with the necessity of giving the patient appropriate medical care. The physician must decide which is more important, keeping the promise of confidentiality to the patient, or providing proper medical care to the patient, which would necessarily entail breaking that promise and telling the mother the truth.

Is the Information Given by the Patient to Be Held in Strict Confidence?

As stated earlier, adolescents seeking treatment for certain conditions, such as sexually transmitted disease, pregnancy or drug/alcohol abuse, can do so without involving the parent or guardian. Physician-patient communications in those settings would be confidential. Thus, if the parent of a teenager with lower abdominal pain secondary to a sexually transmitted infection asks the physician what is wrong with their child, the physician would be bound by confidentiality and could not inform the parent of the patient's condition without the consent of the patient. It is often prudent in those types of situations to strongly encourage the adolescent to involve the parent or guardian, in order to enlist their emotional and other types of support. It has been suggested that if physicians assure confidentiality to adolescents, the adolescents will be more likely to discuss sensitive topics more openly (12). This seems to be true in the case presented.

The American Medical Association agrees with the importance of confidential health care to the well-being of adolescents. They go so far as to say, "When in the opinion of the physician, parental involvement would not be beneficial, parental consent should not be a barrier to care.... The same confidentiality will be preserved between the adolescent patient and physician as between the parent (or responsible adult) and the physician" (13).

If the adolescent is not offered confidential care, there is fear that he or she will be less likely to seek health care in the future when the need arises, with potentially harmful consequences (14).

In the case presented, the physician has promised confidentiality. The only way to maintain this confidentiality would be to have the patient undergo a spinal tap. The immediate risks and discomfort of doing this unnecessary procedure need to be weighed against the potential for future avoidance of medical care. Given those choices, it is likely that the physician will have to break the promise of confidentiality to the adolescent.

Finally, Given the Conflicting Duties, What Should the Physician Do: Act in the Best Interests of the Patient? Respect Patient Autonomy? Tell the Truth? Keep Patient Confidentiality?

Given the conflicting duties facing the physician, a decision had to be made as to the relative importance of confidentiality versus proper medical care. Weddle has suggested that the necessity of confidentiality between the physician and the patient is age dependent. For adults, respect for autonomy necessitates confidentiality in the doctor-patient relationship. For young children, the well-being of the child is assumed to be primarily the concern of the parent, so confidentiality between the child patient and the physician may not be essential to ensure optimal patient care. Adolescents, in this view, fall somewhere in between, and decisions on confidentiality need to be made on a case-by-case basis (6).

Postscript

The physician in this case chose to break confidentiality and tell the parent of the ingestion of dextromethorphan. Informing the parent of the adolescent's drug use may lead to potential intervention in the patient's burgeoning substance abuse problem. Initially, the patient was extremely angry and upset. Eventually, by the time of discharge, the patient admitted that taking the dextromethorphan (and using the parent's credit card to pay for it) had broken the trust that his parents had in him.

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Disaster Preparedness and Triage:

Justice and the Common Good

Robert M. Veatch, Ph.D.

Abstract

"Triage" is a term generally referring to the social practice of sorting or categorizing. While it originally had an innocent, commercial meaning referring to sorting crops according to quality, the term quickly took on a more ominous meaning referring to classifying battlefield casualties into three groups: those too well-off to be treated and then, among those more seriously wounded, one group that will get medical attention and another that will not. The moral problem is how to distinguish between the latter two groups. The Hippocratic oath has been utterly useless in helping us do this sorting, since the oath commands the clinician to remain loyal to the individual patient and give no attention to the choice between two patients with different needs.

Baker and Strosberg show that historically the British sorted following utilitarian principles, giving priority to the patients who could benefit the most even if they were not in greatest need, while the French arranged patients who could be helped in order of greatest need even if it was not maximally efficient to do so. Understanding how contemporary organ transplant policy utilizes triage can help us clarify our mass disaster triage policy. Two organ transplant examples—tissue typing for kidneys and geographical priority for allocating livers—show that American social policy, when forced to choose between allocating on the basis of efficiency or allocating on the basis of justice, will consider both principles, but give equal or dominant priority to justice—even though this priority is understood to be relatively inefficient. Since health care professionals have a recognized preference for efficiency over justice and lay people are inclined towards justice, leaving mass disaster triage policy in the hands of health professionals will predictably structure the policy in a way that conflicts with the moral priorities of the lay population. Formal public debate that recognizes the conflict between efficiency and equity—professional and lay priorities—is therefore essential.

Key Words: Triage efficiency, utilitarianism, equity, justice, kidney allocation, liver allocation, transplantation.

It is with a sense of awe and respect that I come to New York City to talk about the ethics of disaster triage. I lived in the New York area as a child and again for ten years while I was at the Hastings Center in Westchester County. I have always had great affection for this city, and since the fateful September 11 of 2001 that affection has become even more intense.

But why should a moral theorist from Washington come to New York City to talk about the ethics of triage? We had our own smaller scale, but nevertheless horrific, tragedy. From my office window that morning I could see the smoke rising from the Pentagon. But New Yorkers experienced the ultimate case in disaster triage.

In particular, why should a moral theorist whose special area of interest is allocating organs be participating in a conference on the ethics of emergencies and disasters? When I asked her that question, Dr. Rhodes told me that she thought there were important connections between allocating organs and disaster triage. The more I have thought about it, the more that seems right to me.

The Concept of Triage

Most people probably understand the term "triage" from its battlefield use. Its original use was much more innocent. The *Oxford English Dictionary* mentions an 1825 example of sorting coffee beans into three categories: (a) best quality, (b) middling, and (c) badly broken beans called "triage coffee" (1).

By the mid-twentieth century, in World War II, battlefield nurses were dividing the wounded into three categories: (a) those with wounds so minor they do not need immediate attention; (b) those who are critical and can receive significant benefit from immediate attention; and (c) those beyond hope, for whom resources should not be wasted. This battlefield classification still does not, however, explicitly commit to the moral notion of ranking on the basis of using scarce resources where they can do the most good.

By 1974 *Time* magazine was reporting a somewhat more negative sense of the term, stating that triage is "a common sense if callous concept that

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Address all correspondence to Robert M. Veatch, Ph.D., Professor of Medical Ethics, Kennedy Institute of Ethics, Georgetown University, Washington, DC 20057; veatchr@georgetown.edu

Presented at the Issues in Medical Ethics Conference on "Special Challenges of Emergency Medicine" at the Mount Sinai School of Medicine, New York, NY.

teaches that when resources are scarce, they must be used where they will do most good" (2). Here triage is clearly associated with a kind of "utilitarian" reasoning. We should get the greatest possible benefit out of limited resources. We should do so even if it means sacrificing some people who have the greatest need. The priority is for the aggregate good, even if it is unjust or unfair to those in greatest need.

The real story of the ethical principles of triage in disaster is more complicated. It is especially so when health professionals are involved. The complexity can be discerned when one attempts to compare the ethics of triage with the traditional ethic of medicine, the Hippocratic Oath.

The Uselessness of the Hippocratic Ethic

All disaster triage is a violation of the Hippocratic Oath. This is true whether we are considering civilian emergencies or battlefield decision making. The ethic of the Oath, at least as it has been interpreted in modern medical ethics, is simple: the physician's sole duty is to promote the welfare of the patient and to protect the patient from harm. A physician or nurse arriving at a disaster scene would, according to the Hippocratic Oath, take one patient as his or her focus of attention. He or she would take care of that patient until that patient's needs were met and then turn to another patient. In the Hippocratic world it is immoral to let your attention be diverted to others in need, even those who you can help more. The greater needs of another do not permit the Hippocratic physician to abandon the patient under his or her care. Neither does the fact that the physician could do more good *in toto* if the patient of the moment were abandoned.

Fortunately, the Hippocratic ethic has been abandoned by almost all people who have thought about the issues involved (3, 4). It has been abandoned not only for disaster triage, but also for normal clinical medicine. It is a terribly implausible ethic: it requires no informed consent; it has a bizarre confidentiality clause; it has no notion of the rights of patients; and it includes no notion that ethics is social.

Any plausible, more social ethic will open the door to the possibility that a physician can take some limited risks with his or her patient for the good of others in society. For example, with proper consent and monitoring, physicians can engage in research involving human subjects (even though, by definition, research is done for the purpose of producing generalizable knowledge, not for the welfare of the individual patient). Responsible physicians are involved in public health efforts (even though, by definition, these efforts are expended for the health of the public, not the welfare of the individual patient). Some physicians are involved in the procurement of organs for transplants (even from living donors who will not benefit from the surgery, which puts the donor at risk and is certain to cause pain and suffering).

Likewise, responsible physicians respond to mass disaster, even though it requires that they think socially rather than individually. Fortunately, we have outgrown the Hippocratic ethic. The Oath has been abandoned by some. At some schools, it is no longer recited by medical students as they begin their medical careers. It is no longer the foundation of the ethical code of the profession (5). It was decisively rejected when the American Medical Association (AMA) adopted its most recent major revision in 1981 (6). In fact, from its origins, the AMA has always included a dimension of social ethical responsibility in its code of ethics, a perspective totally absent from the Hippocratic tradition (7).

In routine clinical medicine, there may be a case to be made that a clinician ought to provide undivided attention to the patient in front of him or her and let someone else worry about allocating resources (8). Resources have to be allocated; there is no escaping that task. But bedside clinicians may not be the right people to do this. They have been taught throughout their careers that their duty is to their individual patients. When rationing requires a choice between the clinician's own patient and some other persons in need, there is good reason to fear that bedside clinicians will over-commit resources to their own. That is the inevitable outcome of an ethic of loyalty.

Even when they try to take a more neutral perspective, they may be particularly poor allocators. With professional specialization and professional commitment comes a bias in favor one's own area of expertise. Lawyers not only have a self-interest in allocating enormous sums for legal fees; they also really believe that such efforts do great good. Professional artists would want more funds spent on art, clergy on religious activities. It is only natural that clinicians believe that great good comes from clinical activity. These beliefs get incorporated into allocational decisions.

The same occurs within medicine if bedside allocation decisions are made. Cardiologists believe in cardiology; surgeons in surgery; psychiatrists in psychiatry. This probably comes in part from values held before specialization decisions are made. It is confirmed by years of hands-on experience. Clinicians doing bedside rationing would not only have a sense that they are violating the ethic of the profession: they would also be bad rationers.

For all of these reasons, we turn to others to do the allocating. Department heads or administrators or hospital boards may make valid allocational decisions. Perhaps a "triage nurse" in the admitting area can abandon the patient perspective sufficiently to become a good allocator. For the routine case, clinicians beyond that triage point should simply stay with their patients.

While the case for separating clinical and allocation roles makes sense in normal medical care, it makes no sense in a mass disaster. When health professionals arrive on a disaster scene, no one is—in advance—their "patient." Every victim has some kind of presumed moral claim on the nurse's attention. Even for those providing hands-on, one-on-one care it would be immoral to stay with a patient until one literally can do no more—until every bit of good that can be provided has been provided. In a disaster, the moral mandate must be to take only certain patients. It is immoral not to move on after a certain point. This poses a moral dilemma: which patients to take and when to move on?

The Dilemma: Two Principles of Triage

The essence of disaster triage is that many people are simultaneously suffering from many kinds of serious injuries. All of them are drawing upon limited rescue resources. And the limited number of available health care professionals cannot respond adequately to all demands at the same time.

There are two major options—two moral principles. (a) Those victims for whom we can do the most good could be top priority. That approach rests on the utilitarian principle. (b) Alternatively those with the greatest need could be top priority. That approach is based on the principle of justice.

Some with the greatest need are beyond saving. Others with great need can be saved, but doing so will require extraordinary resources. In order to save them, many others with lesser injuries will have to be abandoned. Utilitarians observe that, in some cases, more good can be done in aggregate by targeting those with lesser injuries. Doing the most good for the community of victims would require simply abandoning those who are the worst off. Utilitarians say that that is too bad, but it must be done. Those who would give first priority to the principle of justice reject this option. They would sacrifice the goal of doing as much good as possible. They would let some with minor, but efficiently treatable needs go unattended so that they can do whatever they can for those with the most severe treatable injuries.

While professional health care ethics has generally had utilitarian inclinations, that is not the only option. Many philosophers and many lay people are committed to helping the worst off, even if it means reducing the aggregate good accomplished. This is the ethical perspective of many religious thinkers, including those within the Jewish and Christian traditions (9–11). It is also the perspective of many of today's most respected secular thinkers (12–15).

The Baker/Strosberg Analysis

The most sophisticated analysis of the concept of triage applied to health care is by Robert Baker and Martin Strosberg (16). They note that the British and the French provided two different moral approaches to medical triage.

They attribute the British view to two eighteenth-century physicians, both of whom were associated with the development of the hospital as a place in which to treat the masses. John Aiken and Thomas Percival were concerned about dealing with large numbers of hospital admissions, especially in epidemics such as typhoid. Their principle was to "efficiently optimize outcomes." Influenced by the British utilitarianism of their day, they assumed that the goal was to do as much good in aggregate as possible—to improve mortality and morbidity statistics as much as possible—even if that meant sacrificing some who were among the worst off. This is a perfect example of utilitarian reasoning, consistent with British utilitarian philosophers such as David Hume, Jeremy Bentham, and John Stuart Mill.

This reasoning is also consistent with the normal intuitions of most physicians and other health professionals. The Hippocratic ethic maximizes good for the individual patient. When physicians found themselves in social situations in which they had many potential patients, all needing care at the same time, they simply extrapolated their Hippocratic, benefit-maximizing ethic to the community. Triage ethics in this tradition considers the community of people to be the "patient." The goal is to maximize the good done for the patient group in aggregate.

As a practical matter, this meant classifying patients into three groups: (a) some with injuries too trivial to command immediate attention; (b) some so poorly off that it would be inefficient to treat them; and (c) those who could be treated efficiently if they were given immediate attention. Any utilitarian, including these important eighteenth-century British physicians, could figure out that little benefit would come from treating group (a), and that the maximum benefit would come from giving group (c) priority before group (b).

Baker and Strosberg go on to show that there was an alternative, originating during the Napoleonic wars. Napoleon's surgeon general, Baron Dominique Jean Larrey (1776–1842), was outraged by the unsystematic treatment of battlefield casualties in Napoleon's Grand Army. He developed a system of "sorting" or "triage." Unlike the "British method," however, it was not based on efficiency. "Those who are dangerously wounded must be tended first, entirely without regard to rank.... Those less severely injured must wait until the gravely wounded have been operated on and dressed" (16). The hopelessly dying were left untreated on the battlefield. It made no sense to treat the worst off if it did no good whatsoever. Once that group was set aside, the ranking was based on severity of injury, not on efficiency in treating.

Baker and Strosberg then summarize, pointing out that the surgeon general marched under the banner of "Liberty, Equality, Fraternity." The emphasis was on egalitarianism. Each dangerously wounded but potentially salvageable patient was given a chance. Priority was given to the sickest salvageable patient first. This stood in contrast with the British, who held that those who could most efficiently be made well came first, even if they were not the sickest.

The American Organ Transplant Experience

Similar dilemmas have arisen in the organ transplant world in contemporary times. We know there are fewer organs available than there are people who need them, just as there will be fewer rescue personnel in a disaster than will be needed. In both cases there is nothing realistic that we can do to fully meet all the needs of all who are in need.

In the case of organs, scarcity is inherent. In the case of a disaster, we could potentially put more and more money into disaster preparedness, but at some point it would become irresponsible to siphon off resources so as to be "perfectly prepared." We will never be perfectly prepared for a 9/11 type of catastrophe (or a tsunami). Increasing resources to that point would leave other important projects dangerously underfunded. In the case of organ transplants, we will never be perfectly prepared either. Currently, there are simply not enough organs for everyone who needs one. Even in some ideal future in which many organs will come from non-human sources (e.g., animal organs, artificial organs), the costs of producing enough for every person who could potentially benefit would be staggering. It would mean costs beyond what any society, no matter how rich, would be able to pay.

Two transplant examples may help shed light on how American society has handled the allocation of resources that are inherently scarce. Understanding how our culture contends with the inevitable scarcity in transplant organs may help us understand how we should ration health care in a mass disaster, in which resources will also be scarce. Both examples suggest that public policy tends to favor equality over efficiency.

HLA Tissue Typing for Kidney Transplants

In the 1980s we learned that kidney transplant rejection was related to a system of histocompatability antigens (referred to as HLA antigens). The worse the HLA match, the greater the likelihood of graft rejection. Every kidney recipient has six antigen loci that may potentially match those of the organ donor. Since there are many possible antigens at each locus, the chances of a perfect match are small. Thus, giving an available kidney to the person on the waiting list with the best HLA match would maximize the probability of graft survival, and bring as much benefit as possible from each organ transplanted. By the mid-1990s graft survival with no mismatches was 5% better than with all six antigen loci mismatched (90% vs. 85%, one-year survival) (17). Any good utilitarian would recommend the policy that emerged, of giving an advantage in kidney allocation based on degree of HLA match. (The difference is not as great today, since we have developed better immunosuppression regimens.)

Although this strategy was adopted in good faith, we soon discovered a problem. HLA antigens are racially correlated, and the organ donor pool matched one race better than others. Giving priority based on HLA match de facto meant that one race would get priority over others for kidneys. A black and a white person on the waiting list with equal need would soon have significantly different waiting times for organs.

In addition to race, we learned that other sociological factors predicted a successful kidney graft. One age group did better than others; one socioeconomic group did better; even one gender did somewhat better. If we were consistent utilitarians, we would take all this information into account in allocating organs. We would give kidneys preferentially to young, white middle-class males. The result would be a public system allocating a major health benefit on the basis of race, age, income, and gender.

Health professionals soon realized that this was not acceptable. It was efficient in maximizing benefits, but it was grossly discriminatory. Of course, we would not give an organ to a patient who had no chance of benefiting, but that was not the issue. The problem was that we had reliable data showing that people of a certain age, race, income group, and gender did predictably slightly better. From the point of view of a person with an unusual HLA type (say, one that matched the donor for no antigens), 85% one-year graft survival was attractive. Fairness required giving such persons a right of access, even though we knew on a statistical basis that this patient would not do quite as well as someone with a perfect match. Once we understood this problem, we changed the allocation formula to give blacks and others who were known to match a better chance to receive an organ. We refused to give advantages to higher income people and males, even though we knew they would do a little better. Eventually, partly because of better immunosuppression and partly out of concern for fairness, we almost completely eliminated HLA as a factor in allocating kidneys. Justice held utility in check, at least to a significant extent.

Livers

In the late 1990s, we encountered a similar problem in allocating livers (18). Should a liver go to the sickest salvageable patient or to the one who would benefit the most (even though he is not the sickest)? This controversy played itself out in a debate over whether livers should be allocated on a "locals-first" policy or whether they should go to sicker patients at a regional level before healthier patients in the same community where the liver was obtained.

Three efficiency issues led to the belief that a locals-first policy would be more efficient. First, transporting organs to distant communities with worse-off patients would give organs to patients who, because they were sicker, had less chance of survival. Second, the transportation time would mean greater cold-ischemia time and thus a risk of organ deterioration. Third, there was a fear that if organs went to patients in distant communities, there would be less willingness of people to donate. Hence, the controversy modeled well the choice between fairness (measured in terms of getting organs to those who were worse off) and efficiency (allocating organs locally even though they went to healthier patients).

Transplant surgeons favored the locals-first policy (19, 20). That is exactly what we would predict once we understand that health professionals tend to be utility maximizers. In Hippocratic fashion they attempt to maximize utility to their individual patient and then (by analogy) seek to maximize utility to the community as a whole.

The Clinton administration favored transporting organs to the sickest who could benefit (21). Again, this is what would be predicted from a liberal administration inclined to emphasize greater equality of access to health care. The locals-first policy was thought to be more efficient, but came at the expense of the worst-off patients, who have a chance to benefit. In terms of the Baker/Strosberg account of the history of triage, the British would side with the transplant surgeons in favor of locals first. The French would side with the Clinton administration, which sought equal access across communities.

The result was some degree of compromise, but primarily a victory for the justice perspective. When locals on a waiting list had the highest degree of urgency, they got priority, but regional candidates with the highest degree of urgency took precedence over locals who had less urgent need. That is, public policy tends to favor equality of access, based on need, over efficiency. Clinton's Secretary of Health and Human Services, Donna Shalala, required the national transplant program to rearrange allocation to achieve more equal access. Transplant surgeons were predictably annoyed. Their profession historically has chosen utility-maximizing as the goal. But the American public, influenced by liberal egalitarian concerns, has traditionally favored more equal access.

Implications for Disaster Triage

The implications for a triage plan for a mass disaster seem quite clear. Maximizing aggregate benefit in a disaster plan would divert resources from the sickest in favor of the most efficient to treat. This approach, which requires sacrificing the worst off, is compatible with the traditional core ethic of the health professions, but is incompatible with the liberal political philosophy of the French and American cultures. Our culture's commitment is to liberty and justice for all, not to efficient maximizing of aggregate good. Public policy devoted to the ethical principle of justice or fairness will offer the worst off in the community a chance to be more equal to those who are better off. It will strive to better the lot of the worst off who can be helped, even if that sacrifices some efficiency.

The question, therefore, is whether we should in disaster relief retreat to the utilitarian ethic, making an exception to the ethic of justice that generally prevails in American ethics. In doing so, we would follow the utilitarian ethic of the British and the historical biases of the medical profession. Or should we adhere to the classical moral commitment of the French and American revolutions, the ethic of the Judeo-Christian tradition and its secular, justice-oriented analogues? This would give a priority to the worst off, even if it is inefficient to do so.

The Deliberations of the UNOS Ethics Committee

The Ethics Committee of the United Network for Organ Sharing (UNOS) took up the question of whether allocation should be utilitarian or justice-based. The result could be predicted by anyone who knew the historical tendencies of health professionals and lay people when it comes to this controversy. The committee was split right down the middle.

Half the committee wanted to give kidney tissue typing high priority. They wanted to consider HLA as a predictor of good outcome and also wanted to keep livers for local use. The other half wanted fairer allocation, downplaying tissue typing in kidney allocation and giving livers to sicker patients beyond the local level. This division of opinion reflected the division in committee membership: there were equal numbers of surgeons and lay people.

Every physician on the committee favored utilitarian allocations. Every non-physician favored justice-based allocation. Leaving triage policy to one group or another will predetermine the policy. For organ transplant, the UNOS Ethics Committee explicitly negotiated a political compromise. Justice theorists insisted on an absolute priority for needs-based allocation. Surgeons insisted on an absolute priority for maximizing benefits. (There were no non-surgeon physicians on the committee at the time.) A compromise was reached whereby utility and justice would have equal priority in formulas to allocate organs.

Leaving policy formation to health professionals or lay people will predetermine what the triage policy will be. There should be a full-scale public debate about how we will balance efficiency and equity in our disaster triage policy. Perhaps the outcome will be a political compromise in which no one will be completely satisfied. The result is likely to include a willingness to ignore the cries of the worst off when intervention is certain or very likely to fail. There will also be a willingness, especially among lay people, to target resources for the worst off who can be helped. There will also be a concern about efficiency, especially among health professionals, and a desire that scarce health resources not be squandered.

In various situations, the Americans have sided alternatively with the British and the French models of triage, with concern for utility and for justice. Both concerns deserve a hearing when a disaster policy is made explicit.

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The Ethics of Research without Consent in Emergency Situations

Lynne D. Richardson, M.D.

Abstract

In 1996, the federal government published regulations that allow investigators to obtain a waiver of informed consent for emergency research when certain very specific criteria are met. The participants must be unable to give consent as a result of their medical condition, and the intervention involved in the research must be administered before consent from the participants' legally authorized representative is feasible. These regulations require that a number of special protections be provided whenever such a waiver is obtained. Before the study is performed, there must be "community consultation" and "public disclosure." The regulations leave the specific form and extent of these activities to the discretion of the Institutional Review Board granting the waiver of informed consent and the investigator conducting the study. The author reviews the development of these regulations, often referred to as "The Final Rule," the ethical basis for the waiver, and the specific provisions of the federal regulations that govern research without consent in emergency situations. Reactions of proponents, critics and the lay public are discussed.

Key Words: Community consultation, emergency medicine, emergency research, exception to informed consent, human experimentation, informed consent, resuscitation research, research ethics, public access defibrillation, waiver of informed consent.

Introduction

THE FRUITS OF RESEARCH are all around us. The products of science have affected every aspect of our lives: the food we eat, the clothes we wear, and certainly, the medical care we receive. As George Annas has asserted, "the history of medical progress is to a large extent the history of medical experimentation" (1). The history of medical experimentation, however, is not one of unblemished glory. The administration of potentially harmful substances and procedures to individuals without their consent is a practice as old as medicine itself. The earliest documented abuses of human rights in the name of science go back to 137 BC, when Attalus III of Pergamum experimented with poisons and antidotes on condemned prisoners (2). In the U.S., the history of medical research atrocities stretches from the surgical experiments of Dr. J. M. Sims on female slaves in the 1840s (3) to the infamous Tuskegee Syphilis Study (4, 5), and the U.S. Department of Energy studies of ionizing radiation (6).

Despite these and many other documented incidents around the world, the abuse of unsuspecting and vulnerable individuals in the name of research did not become the focus of worldwide attention until the middle of the last century. Public outrage over the experiments of Nazi doctors on concentration camp victims led, in 1947, to the Nuremberg Code, a codification of the basic human rights of research subjects that was included in the judgment of the Nuremberg Tribunal (7). This set of standards proclaimed voluntary consent of the subject, prior to participation in research, as an absolute requirement for ethical research. In 1964, the World Health Organization's Declaration of Helsinki reaffirmed the protection of individual autonomy through the informed consent process, although this document allowed for consent by surrogates on behalf of impaired individuals who were incapable of giving consent themselves (8). In this country, the Belmont Report was issued in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (9). This document has served as the ethical basis for U.S. federal regulations on human subjects research.

Associate Professor of Emergency Medicine, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Lynne D. Richardson, M.D., F.A.C.E.P., Emergency Medicine, Box 1620, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: Lynne.Richardson@mssm.edu

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The Ethical Basis of Research

The Belmont Report identifies three ethical principles relevant to the conduct of research: respect for persons, beneficence and justice. Respect for persons, in the case of individuals capable of making decisions for themselves, requires respect for their autonomy. Conducting research on such individuals without their knowledge and consent is a violation of their autonomy. Respect for persons also requires that individuals who lack the capacity to give informed consent be protected from the risks of research. The principle of beneficence imposes a duty on the researcher to maximize benefits and minimize risks to individuals participating in research, as well as to obtain knowledge that may benefit others. The principle of justice requires that the burdens of research be shared equitably among those who will share in the benefits of research.

By the beginning of the 1980s, obtaining prior voluntary informed consent had become the ethical cornerstone of research. On the federal level, both the Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA) promulgated regulations requiring voluntary informed consent from all research subjects or their legal surrogates (10, 11). Institutional Review Boards (IRBs), which were charged with local responsibility for protecting the rights of human subjects participating in research, focused most of their attention on assuring the integrity of consent processes. At that time, there was only one category of studies for which a waiver of informed consent could be obtained. Only studies that were judged to involve minimal risk to participants and which could not be practicably conducted without a waiver of informed consent were eligible for such a waiver. The regulations specifically defined minimal risk as risk in which "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests" (10).

The Special Challenges of Emergency Research

The development of emergency medicine and critical care as academic specialties during the 1980s led to a surge in research on patients suffering from critical illnesses and injuries. These studies presented a challenge to the federal research regulations, since often the medical conditions being studied rendered the patient unconscious or unstable (e.g., cardiac arrest, profound shock, severe head trauma, etc.). Moreover, the treatments under study had to be administered in a time frame that made obtaining the consent of surrogates problematic. This was particularly true in the emergency department, where treatment, whether standard therapy or experimental, would often have to begin before relatives of the victim had been located and notified (12–14). In the pre-hospital arena, there was often no IRB oversight of EMS (emergency medical services) research, and obtaining consent from subjects was often not part of the research protocol (15).

Both investigators and those responsible for overseeing investigators (e.g., IRBs and federal regulators) struggled with the practical and ethical issues raised by such studies (16–18). Clearly, the regulations at that time made no provision to allow research to be conducted on critically ill or injured patients without consent from the patients or their surrogates. However, the dismal prognosis of most of these conditions created an imperative for research that the scientific establishment found difficult to ignore. A number of mechanisms were proffered to allow such research.

One approach was to more broadly interpret the provisions of the "minimal risk" waiver, to allow the study of experimental therapies with significant risk. The argument was made that these risks were "ordinary" for individuals with life-threatening conditions (19). Some authors call this concept "minimal *differential* risk" (20). Another approach was to reference the FDA regulations on exception from informed consent for emergency treatment using a "test article," a regulated drug or device that is being studied (11). Although these regulations clearly state that they apply to emergency *treatment* without consent, they were used by many IRBs and by the FDA itself to define circumstances under which prospectively designed *research* could take place without consent (21).

Some investigators explicitly acknowledged that the extant research regulations regarding informed consent were inadequate to address the issues raised by clinical trials in emergency care and resuscitation research. The often-insurmountable obstacles to obtaining prospective informed consent when studying individuals suffering from a sudden, devastating, clinical condition gave rise to a concept called "deferred consent" (20, 22). This concept permitted investigators to enroll patients in studies to test emergency treatments for critical medical conditions without consent. Subsequent to initiation of the experimental protocol, consent would be obtained from either the patient or their surrogate, to continue participation in the research. Critics argued that consent after-the-fact was not consent at all, so the term "ratification" was preferred by many (23, 24). A number of large, federally funded studies were approved by IRBs using this mechanism (20, 22).

Throughout the 1980s and early 1990s, the broadened definition of "minimal risk," the FDA exception to treatment rules, and the concept of deferred consent were used to address the issues raised by resuscitation and emergency research. Although these mechanisms were a clear departure from the letter of the regulations, they were attempts by investigators and IRBs to address the ethical and regulatory issues while allowing research that was seen as necessary and justified to proceed. No attempt was made to change these regulations, despite the widely held belief that they simply did not address the complex issues surrounding consent in emergency situations (24). Officials from the Office for Protection from Research Risks and the Food and Drug Administration acknowledged, and in some cases supported, the use of these mechanisms by IRBs to permit research without prospective informed consent (18).

Suddenly, in August of 1993, all of this was brought to an abrupt halt. The Director of the Office for Protection from Research Risks issued a "Dear Colleague" letter stating that "all human subject research approved by IRBs and all studies funded by the National Institutes of Health (NIH) require prospective informed consent from the patient or their legal representative" (25). The letter expressly prohibited the use of deferred consent and required the literal interpretation of the "minimal risk" regulations. The OPRR instructed that studies previously approved using these mechanisms be stopped and stated that IRBs would be held responsible if they permitted any study to proceed without prospective informed consent.

The OPRR Director's letter was prompted by a number of events. Revelations in the lay press about radiation experiments conducted decades earlier by the U.S. Department of Energy triggered a directive to investigate current research regulations (26). A written inquiry by an IRB considering the PEG-SOD Clinical Trial protocol, a study of the free radical scavenger polyethylene glycol superoxide dismutase for traumatic coma, specifically asked about the congruity of deferred consent and the OPRR regulations (21, 24). The U.S. House Subcommittee on Regulation of Small Business and Technology released a report itemizing complaints from those who were participants or family members in several studies that used deferred consent, and the subcommittee's chairman promised a public hearing to expose unethical behavior by the research community (27). It is within this political context that OPRR issued its letter requiring strict enforcement of the regulations. As a result, several large trials were stopped mid-stream and a moratorium on resuscitation and emergency research was begun (24, 28).

Concerned members of the research community, fearing a permanent end to important research in resuscitation and emergency care, organized themselves into the Coalition of Acute Resuscitation and Critical Care Researchers (29). This Coalition included representatives from emergency medicine, cardiac care, neurotrauma and critical care medicine, as well as patient advocacy groups, the bioethics community and IRBs. Observers from the FDA and OPRR, and staff members from Senate and House committees with relevant jurisdiction also participated in Coalition discussions. A consensus statement articulating the ethical and operational issues that must be addressed in studies of critically ill or injured patients was developed (30). The consensus statement emphasized patients' rights and the special need for protection of this vulnerable, acutely ill population.

In January 1995, the Coalition Consensus Document was presented at a public forum convened by the NIH and the FDA on "Informed Consent in Clinical Research Conducted in Emergency Research Circumstances" (31). After considering the testimony offered at the public forum, and multiple discussions with the Coalition and other stakeholders, a Proposed Rule for Waiver of Informed Consent for Emergency Research Circumstances was signed by the Commissioner of the FDA and the Secretary for the Department of Health and Human Services in August of 1995. After widespread circulation, public comment and some revision, the "Final Rule" (referred to as the Waiver of Informed Consent Requirements in Certain Emergency Research in the DHSS regulations and the Emergency Exception to Informed Consent in the FDA regulations) went into effect in November, 1996, ending the three-year moratorium on emergency research (32).

The Emergency Research Consent Waiver

The new regulations define specific circumstances under which a waiver of informed consent for emergency research can be obtained: "The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions" (32). Several additional criteria must be met: the medical condition being studied must render the subject unable to give consent, the intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible, and there is no reasonable way to prospectively identify individuals likely to become eligible to participate. Furthermore, the research must offer the prospect of direct benefit to participants and there must be no practical way to carry out the research without the waiver.

The regulations specify a number of special obligations for the investigator and for the IRB reviewing the waiver application, to provide additional safeguards. These include a requirement for consultation with the community in which the research will be conducted and from which the subjects will be drawn; public disclosure to the community(ies), prior to the initiation of research, of the risks and expected benefits; public disclosure after completion of the study of the results and the demographics of the participants; and an independent data-monitoring committee. The major features of the regulations are summarized in the Table.

Proponents of the new regulations argue that they adhere to the ethical principles outlined in the Belmont Report. They contend that the waiver of consent does not infringe upon the autonomy of participants; the life-threatening medical condition from which they are suffering has already deprived the participants of their autonomy (28, 33). The principle of respect for persons demands that these individuals be treated as vulnerable persons whose interests need to be protected. It has been suggested that, just as the requirement for informed consent for *treatment* is routinely suspended in such emergency situations, the requirement for informed consent for *research* may also be suspended (18, 28). This logic is not entirely persuasive. In the case of emergency treatment, patients are presumed to want life-saving treatment, and health care providers act under the doctrine of presumed consent. While it is true that not all patients in all situations consent to life-saving treatment, the exceptions are so few and so narrowly circumscribed that the practice of *treating* patients in emergency situations without consent is universally accepted as an ethical practice.

TABLE

Summary of Requirements for Waiver of Informed Consent in Emergency Research

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The human subjects are in a life-threatening situation for which:
- available treatments are unproven or unsatisfactory
- valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions.

Obtaining informed consent is not feasible because:
- the subjects will not be able to give their informed consent as a result of their medical condition;
- the intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and
- there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

Participation in the research holds out the prospect of direct benefit to the subjects.

The research could not practicably be carried out without the waiver.

The investigator must attempt to contact a legally authorized representative or family member for each subject within the potential therapeutic window, if feasible.

The IRB has reviewed and approved informed consent procedures and documents.

Additional protections are provided:
- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;
- Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
- An independent data-monitoring committee exercises oversight of the research.
- At the earliest feasible opportunity, each subject, or their surrogate, shall be informed of the subject's inclusion in the research, the details of the research and that he or she may discontinue the subject's participation at any time.

There is no consensus about the presumed preference of an individual who is unable to consent to research. Many believe in "the right of all individuals not to be used as research subjects without their consent or the consent of those who speak for them" (34). However, this presupposes that participation in research is not in the individual's best interest. It may be that "participation as a research subject is an essentially altruistic act. The subject allows one's being to be used as a data source, contributing to...medical knowledge" (33). However, it is also true that patients who are critically ill or injured and who are at high risk of morbidity or death "might be in greatest need of innovative therapy" (33, 35). As one author put it: "There is an irreconcilable conflict between such an individual's right to be protected from interventions he or she would not want, and the right to have access to interventions that he or she would want" (36). Furthermore, in a setting where certain death is the expected clinical outcome, an opportunity to benefit future patients might be an individual's preference even when no benefit to oneself is expected. Thus it would seem that summarily prohibiting research without consent might be as much a violation of patient autonomy as requiring such participation.

The regulations attempt to limit the waiver of informed consent to situations where both the research participants and future patients are likely to benefit. By limiting the waiver to lethal conditions for which no good treatment exists, to interventions that have scientific data supporting their potential effectiveness, and to protocols that hold out the prospect of direct benefit to the participants, the rule defines a narrow window within which research participation might be presumed to be the choice of most individuals. Under these conditions, the principle of respect for persons would therefore support research participation without consent, on the same basis that it supports emergency treatment without consent. However, because of the greater potential for the goals of research to diverge from the interests of the individual, these vulnerable individuals are afforded several other protections. The provisions requiring attempts to notify surrogate decision makers, the requirement for an independent data-monitoring committee and the special provisions regarding community consultation and public disclosure all serve this purpose of protecting the interests of the participants.

Proponents argue that the principle of beneficence is also clearly followed in the regulations. This principle requires physicians and researchers to act in the best interests of both present and future patients. The grim prognosis associated with many emergency conditions provides a compelling force to find and test better treatments for future victims. If promising new therapies can be tested while protecting the interests of research participants, "it would sometimes be unethical not to conduct research that could ultimately benefit those most in need" (33). The regulations require "clinical equipoise": that is there must be scientific evidence that the experimental therapy is at least as effective as existing therapies. The independent data-monitoring committee assesses the continuing necessity and value of the research while assuring the safety of the participants.

Provisions to ensure the third relevant ethical principle, justice, were also included in the regulations. Community consultation is required with the community from which the subjects are drawn; public notification prior to and after the study, and the specific requirement to disclose the demographics of the participants are all designed to prevent abuses by researchers. In summary, many feel that these regulations allow necessary research to proceed while providing maximal protection for the research participants. Thus, significant support for the "waiver of informed consent for emergency research" rule has been voiced in the emergency medicine, critical care, and trauma literature (24, 37–39).

Critics of these regulations have been equally vocal; calls to rescind the regulations have also appeared in the literature (40–43). In the words of one author, the waiver rules "represent a triumph of the interests of the pharmaceutical industry, medical device companies and the research community...over the therapeutic interests of present patient-subjects as well as society's interests in limiting the authority of the state and investigators to conscript subjects for research without their consent" (40). Others predict that research without consent will be disproportionately practiced on minority populations because of their disproportionate use of emergency departments and the increased prevalence of conditions such as heart disease, stroke, and firearm injury within these populations (43).

On the other side, researchers have condemned the regulations for being too narrow, too vague and too onerous (37, 44–46). Many issues are unclear. For example, the waiver is restricted to "life-threatening conditions." Certainly cardiac arrest, which carries a mortality rate of 80–98%, is "life-threatening." What about a condition with 50% expected mortality? What about a condition with 10% expected mortality? At what level of expected mortality does a condition become "life-threatening"?

Early experience with the waiver revealed that the provisions regarding community consultation and public notification are most problematic (47, 48). Appropriately identifying and effectively communicating with the relevant "community" or communities is a formidable, expensive and often unsuccessful undertaking (49, 50). Many researchers tend to approach the concept of community from an operational perspective. That is, they often conceptualize the relevant "community" to be consulted as the population of eligible subjects from which research participants will be drawn. Certainly, those who are most directly involved in the research as participants, or as family members or providers of participants, must be consulted. But both the regulations and the ethical principles underlying them require some broader definition of "community"; it cannot be limited to a cohort of eligible subjects. One can easily imagine a research protocol that would be widely regarded as deplorable but was acceptable to a small group of eligible individuals made desperate by their circumstances.

While for some there is a great deal of intuitive appeal in the notion of community consultation and notification as a surrogate for informed consent, for others it conjures up the memory of "community" as used by the totalitarian fascist and communist regimes of the last century. Just as the larger community must sometimes protect the interests of eligible subjects, the interests of the eligible subjects may need to be protected from the larger community.

Critics of the 1996 regulations have decried the lack of specificity of the regulations, the confusion between "community consultation" and "public disclosure," and the sometimes prohibitive costs of complying with the rule. The number of studies that have sought a waiver under the new rules is lower than expected by many, perhaps in part due to the difficulties in complying with the protective provisions (41, 44, 45). Proponents argue that the language is purposefully vague to allow individual investigators and IRBs to determine what is appropriate on a study-by-study basis. Attempts to provide guidance to investigators have been made by the Department of Health and Human Services as well as by a number of individual authors (48, 51–56). Over the past few years, a number of investigators have successfully obtained community consultation and provided public disclosure under the 1996 regulations (37, 48, 56–62).

The PAD Clinical Trial was an NIH-funded, multi-center study of Public Access Defibrillation (PAD), a comprehensive, integrated community approach in which laypersons are trained to use automated external defibrillators (AEDs) to treat individuals who collapse in cardiac arrest in non-hospital settings (61). Since obtaining informed consent from the patient or a surrogate is untenable in the case of sudden cardiac arrest, the PAD protocol was approved with a waiver of informed consent for emergency research by 101 separate IRBs in study sites in the U.S. and Canada. The recently published IRB experience of the PAD investigators exemplifies the special challenges faced by multi-center studies under the current regulations (63, 64).

Despite the innovative inclusion of community consultation and public disclosure in the regulations, very little input from the community has been sought in the ongoing debate. In 1997, Smithline and Gerstle published a small survey of ED patients' attitudes towards waiver of informed consent (65), in which 212 patients were presented with two research scenarios and asked if they would want to be enrolled without their consent. Of the 212 patients, 73% favored a study that involved minimal risk and no benefit (i.e., having an extra blood test), a study that would not be permitted under the emergency research consent waiver (which requires the potential for direct benefit to participants). Only 50% approved of a study that provided potential benefit but involved more than minimal risk (i.e., administrating a novel medication with known serious but unlikely side effects). These data suggest that there is significant discordance between the regulations as written and the attitude of potential research participants.

Investigators are continuing to explore the attitudes of the general public towards research without consent. The *Community VOICES* Study (C*ommunity* V*iews On* I*nformed* C*onsent in* E*mergency* S*ituations*) (66) is a mixed-methods exploration of community attitudes towards the current regulations and the underlying ethical principles. Do community members think the waiver should be limited to life-threatening conditions? Do they think the potential for direct benefit is essential? And perhaps most important, how does one identify the appropriate and relevant community for purposes of consultation and disclosure regarding research without consent? The *Community VOICES* study is currently gathering empirical data to address these questions.

Conclusion

The evolution of research ethics over the past 50 years has centered on informed consent as essential to the conduct of ethical research. The special challenges of emergency medicine and critical care research led to a special set of regulations that define conditions under which research can be ethically conducted without obtaining prospective informed consent from participants. The appropriateness and adequacy of the current regulations continue to be debated within both the ethics and research communities. It is not yet known whether lay community members endorse the conduct of research without consent or whether they endorse the current provisions of the emergency research consent waiver regulations.

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Grand Rounds

Monoclonal Antibodies, Immunogenicity, and Associated Infusion Reactions

ADAM CHEIFETZ, M.D.[1], AND LLOYD MAYER, M.D.[1,2]

Abstract

The increasing use of monoclonal antibodies as treatment modalities for a number of immune mediated and malignant diseases has yielded great promise. In using this approach, however, we have encountered problems, in terms of infusion reactions. Two forms of reactions have been identified: acute and delayed; they appear to be related to the presence of antibodies to the monoclonal antibodies (against murine or human components). The reactions are largely **not** anaphylactic (IgE mediated), making it possible to re-treat patients using specific protocols. These protocols are detailed in this overview.

Key Words: Monoclonal antibody, inflammatory bowel disease, infusion reactions, infliximab.

Introduction

A NUMBER OF NEW BIOLOGIC THERAPIES that have become available over the last 15 years have revolutionized the treatment options for immune mediated inflammatory diseases (e.g., rheumatoid arthritis [RA], Crohn's disease [CD], and psoriasis). The most notable of these agents is infliximab, a chimeric (part-murine, part-human) monoclonal antibody that binds to tumor necrosis factor alpha (TNF-α) and neutralizes its biologic activity. Infliximab has been shown to be effective and safe in the treatment of moderately and severely active and fistulizing CD, RA, ankylosing spondylitis, uveitis, and pyoderma gangrenosum (1 – 12). Infliximab was approved for the treatment of CD in 1998 and for RA in 1999.

As is the case with any foreign-protein-derived agent, infusion of infliximab can lead to infusion reactions, either acute or delayed. Overall, these reactions are rare, occurring in approximately 5 – 10% of all infusions, and they can, in most cases, be easily managed (13). Although the mechanisms underlying the development of infusion reactions are not completely understood, antibody formation against infliximab may play a role. The generation of antibodies to these monoclonal antibodies is currently an area of intense research. It has recently been shown that the formation of antibodies to infliximab is very likely to be associated with a greater risk of infusion reactions and that it may also limit infliximab's long-term efficacy (14, 15). However, new infusion techniques and approaches have been developed that may minimize such antibody formation and mitigate its potentially negative effects. Such methods should now be considered for all routine infliximab infusions in order to help maintain the efficacy of infliximab and reduce the potential side effects associated with antibody formation.

Immunologic Basis for Infusion Reactions

Many of the new biologic therapies now available for treatment of immune mediated inflammatory diseases are monoclonal antibodies. These antibodies are designed to block particular factors involved in the inflammatory pathway. This is accomplished by binding to and neutralizing/elimi-

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From the [1]Division of Gastroenterology, and [2]the Immunobiology Center and Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Lloyd Mayer, M.D., Immunobiology Center, Box 1089, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; email: lloyd.mayer@mssm.edu

Adam Cheifetz, M.D., is currently at Beth Israel Hospital, Boston, MA.

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nating individual cytokines or triggering the death of cytokine-producing cells. Like all immunoglobulins, these engineered antibodies are comprised of an Fab fragment that includes the antigen-binding domain and an Fc portion that binds complement and Fc receptors on phagocytic cells. Monoclonal antibodies are classified according to the amount of murine protein present in the molecule. When murine protein is present, it partially or fully makes up the antigen-binding domain of the antibody. There are four types of monoclonal antibodies that are used in clinical practice today (Table 1). Murine antibodies, such as OKT3, are comprised entirely of murine protein. Human antibodies, such as adalimumab, are devoid of all murine protein. Monoclonal antibodies rituximab and infliximab are examples of chimeric antibodies, of which 25% is murine and 75% is human. Humanized antibodies, of which CDP-571 is an example, are 15% murine (specifically the antigen-binding domain) and 85% human. Although distinct in their composition, all four subtypes have been utilized successfully as clinical therapies.

The human immune system typically reacts to these monoclonal antibodies as foreign antigens and responds by creating its own antibodies to different sites on the molecule. If murine protein is present in the monoclonal antibody, the immune system can react by producing anti-idiotypic, anti-allotypic, or anti-mouse antibodies. As would be expected, monoclonal antibodies comprised entirely of murine protein are more likely to elicit an immune response than completely human monoclonal antibodies. However, even completely human monoclonal antibodies can trigger an immune response, leading to the development of human anti-human antibodies (HAHA).

Two companies have developed an assay for antibodies to infliximab. This assay is able to measure anti-murine antibodies (to epitopes on the murine variable region of infliximab) as well as anti-allotypic antibodies to the human immunoglobulin G1 (IgG1) constant region. When this assay has been used in individuals receiving infliximab infusions, only anti-murine antibodies have been found (16). These antibodies were originally known as human anti-chimeric antibodies (HACA) but now are more commonly known as antibodies to infliximab (ATI). Since infliximab itself interferes with the ATI assay in one assay system, the presence of these ATI can only be determined when infliximab is not detectible in the serum. When infliximab is found in the serum, the sample is considered indeterminate. It has been proposed that it may be reasonable to consider samples that are indeterminate for ATI as negative, because even if present, these ATI are overwhelmed relative to concentration of infliximab (16).

TABLE 1

Classification of Monoclonal Antibodies

Type	% Murine	Example
Human	0%	adalimumab
Humanized	15%	CDP-571
Chimeric	25%	infliximab
Murine	100%	OKT-3

Types of Infusion Reactions

Infusion reactions to infliximab or against any monoclonal antibody can be characterized as either acute or delayed. An acute infusion reaction occurs within 24 hours of an infliximab infusion, but most commonly within 10 minutes to 4 hours of the infusion. A delayed infusion reaction can occur from 24 hours to 14 days after an infusion of infliximab, but usually occurs after 5–7 days. Both types of reaction can be further characterized as mild, moderate or severe, depending on the accompanying signs and symptoms (Table 2).

Acute infusion reactions can also be characterized by whether they are anaphylactic or non-allergic based, i.e., IgE-mediated type I acute hypersensitivity (anaphylactic) or anaphylactoid. Symptoms of true allergic anaphylactic reactions include chest tightness, shortness of breath, flushing, hypotension, wheezing and urticaria. In fact, without bronchospasm or urticaria, an acute infusion reaction is unlikely to be a true type I mediated hypersensitivity reaction and should be considered non-allergic. The non-allergic types of reactions make up the overwhelming majority of acute infusion reactions.

To date, only one study has examined the pathogenesis of acute infusion reactions (13). In this study, performed at Mount Sinai, serum was obtained from eleven patients who had a total of fourteen acute infusion reactions. The level of tryptase, a mast cell enzyme elevated after an acute hypersensitivity reaction, was measured and found to be within the normal range in all cases. Levels of IgE were evaluated in six of these patients and were also found to be normal. It was concluded that these acute infusion reactions were not due to IgE-mediated hypersensitivity. This probably explains why most of the reactions were successfully managed by simply reducing the rate of infusion (13). If these had been IgE mediated anaphylactic reactions, re-infusion would have been impossible.

Delayed infusion reactions are characterized

TABLE 2

Infliximab Infusion Reaction Protocol *

Type of Reaction Symptoms	Treatment Protocol	Prophylaxis
Mild		
Flushing, Dizziness, Headache, Diaphoresis, Nausea, Palpitations	Slow infusion rate to 10 mL/hr Infuse normal saline (500 – 1000 mL/hr) Diphenhydramine 25 – 50 mg IVPB Acetaminophen 650 mg Monitor VS every 10 min, until WNL Wait 20 min, then increase infusion rate to 20 mL/hr × 15 min, then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated	Pre-treat with diphenhydramine 25 – 50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated.
Moderate		
Chest discomfort, SOB, Hypo/hypertension (>20 points SBP), Increased temperature, Palpitations, Urticaria	Slow infusion rate to 10 mL/hr or stop infusion Infuse normal saline (500 – 1000 mL/hr) Diphenhydramine 25 – 50 mg IV Acetaminophen 650 mg Monitor VS every 5 min until WNL Wait 20 min, then restart infusion at 10 mL/hr for 15 min Increase infusion rate to 20 mL/hr ×15 min., then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated	Pre-treat with diphenhydramine 25 – 50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior x15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated.
Severe		
Hypo/hypertension (>40 points SBP), Increased temperature with rigors, Chest discomfort, SOB with wheezing, Stridor (if potential to lose airway, call EMS for transport to ER), Flushing	Stop infusion Infuse normal saline (500 – 1000 mL/hr) Maintain airway; oxygen if available Epinephrine (1:1000) 0.1 –0.5 mL SQ (may repeat q 5 min ×3) Diphenhydramine 25 – 50 mg IVPB Hydrocortisone 100 mg IV or methylprednisolone 20 – 40 mg IV Monitor VS every 2 min until WNL If patient stabilizes, wait 20 min, then restart infusion at 10 mL/hr for 15 min Increase infusion rate to 20 mL/hr ×15 min, then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated If patient requires second dose of epinephrine, call EMS and transfer patient to ER for monitoring	Prednisone 50 mg PO q12 hours BID × 3 doses prior to infusion or Hydrocortisone 100 mg IV or methylprednisolone 20 – 40 mg IV prior to infusion. Pre-treat with diphenhydramine 25 – 50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior ×15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr every 15 min, as tolerated.
Delayed		
Rash / urticaria, Myalgias, Flu-like symptoms, Joint stiffness and pain, Headache	Acetaminophen 650 – 1000 mg PO QID Second generation antihistamine or diphenhydramine 50 mg QD-BID Medrol pack if severe joint pain	Pre-treat with diphenhydramine 25 – 50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase rate to infuse over 3 hours. Acetaminophen 650 – 1000 mg PO QID × 3 days post infusion. Second generation antihistamine × 7 days post infusion. Send home with Medrol dose pack if severe joint pain.

EMS = emergency medical services; ER = emergency room; IVPB = intravenous piggyback; VS = vital signs; SBP = systolic blood pressure; WNL = within normal limits; SQ = subcutaneous; SOB = shortness of breath.

* If patient experiences a second reaction during the infusion, follow steps for moderate reaction, but give IV hydrocortisone or methylprednisolone. Do not increase rate past where the patient had the reaction.

by a skin rash, diffuse joint pains, fatigue and myalgias, with or without fever. These reactions have been labeled "serum-sickness-like" and may actually represent mild type III (immune-complex-mediated) reactions. We previously proposed the term "delayed immune-mediated infusion reaction." Regardless of the terminology, delayed infusion reactions must be differentiated from other states that may produce similar symptoms such as an inflammatory bowel disease (IBD) flare, extra-intestinal manifestations of IBD, a viral syndrome, or a lupus-like reaction.

Management of Infusion Reactions

The management of acute infusion reactions should focus on alleviating the patients' associated signs and symptoms (i.e., fever, chest pain, and dyspnea). Such symptoms usually resolve with adjustment of the infusion rate and administration of intravenous fluids, acetaminophen, antihistamines and steroids. (Epinephrine is indicated when wheezing is present.)

A suggested infliximab infusion reaction treatment protocol, based upon the experience at Mount Sinai, has been published previously and is slightly modified here (Table 3). These modifications are based on continued clinical experience in treating and preventing infusion reactions. The importance of saline infusion in patients experiencing an infusion reaction cannot be understated. It is also extremely important to auscultate the lungs if the patients are complaining of chest pain and shortness of breath. The absence of wheezing virtually rules out a true anaphylactic reaction.

Severe anaphylactic reactions are rare, but if they occur, the infusion should be stopped immediately, normal saline should be infused, and vital signs should be monitored every 2 minutes. Epinephrine 0.1–0.3 cc should be administered subcutaneously and repeated two more times at five-minute intervals if needed. Intravenous diphenhydramine (25–50 mg) and steroids (either hydrocortisone 100 mg or methylprednisolone 20–40 mg) should also be given, as well as PO acetaminophen (650–1000 mg). The epinephrine and diphenhydramine should be given before the steroids because of their faster onset of action. In these rare cases of anaphylaxis, the infusion should not be restarted. These patients may be eligible for desensitization or an experimental protocol using adalimumab (fully human anti-TNF antibody).

The vast majority of reactions are not IgE mediated and respond to stopping the infusion and providing hydration, diphenhydramine and acetaminophen. Patients in this group may have their infusion restarted slowly after 30 minutes. By slowing the rate of infusion, the opportunity for soluble immune complexes to form is greatly reduced. Development of an infusion reaction does not preclude further infliximab infusions. Pretreatment (prophylaxis) protocols were developed using previous desensitization protocols for 5-fluorouracil and vancomycin as templates. For prophylaxis in mild or moderate acute reactions, the patients should receive diphenhydramine (25–50 mg) and acetaminophen (650 mg) orally 1.5 hours prior to infusion. Alternatively, the patients can be given a second-generation non-sedating antihistamine for five days leading up to the infusion, in order to avoid the sedating effects of diphenhydramine. If a test dose of infliximab (10 mL/hr) is tolerated, the infusion rate should then be increased every 15 minutes to 125 mL/hour as tolerated and continued for at least 3 hours (Table 4). For severe acute (non-IgE mediated) reactions, in addition to an antihistamine and acetaminophen, the patients should receive prednisone 50 mg × 3 doses over 24 hours prior to the infliximab infusion. Alternatively, intravenous hydrocortisone (100 mg) or methylprednisolone (20–40 mg) could be given 20 minutes before infusion, although this is probably less efficacious. A maximum infliximab infusion rate of 125 mL/hr should not be exceeded in these patients.

In our study, after receiving the appropriate medical prophylaxis, all of the patients who had mild or moderate acute infusion reactions tolerated re-treatment and completed re-infusion with infliximab when clinically indicated. One patient with a moderate infusion reaction early in the study was not re-treated because of our limited experience at

TABLE 3

Methods of Decreasing Antibody Formation to Infliximab

1. Use concurrent immunomodulator (6-MP, azathioprine, or methotrexate)
2. Induction (0, 2, and 6 week or 0 and 4 week) and maintenance (q 8–12 weeks) infusion regimen
3. Steroid pre-medication prior to infusion, if not on immunomodulator (i.e., intolerant)

6-MP = mercaptopurine

TABLE 4

Methods of Combating Antibodies to Infliximab

1. Add immunomodulator if patient is currently not taking
2. Increase the dose of infliximab by 5 mg/kg
3. Slow infusion rate (i.e., infusion over 4–6 hours instead of 2 hours)
4. Shorten the infusion interval (i.e., every 4–6 weeks)
5. Switch to another anti-TNF agent (e.g., adalimumab)

TNF = tumor necrosis factor

that time. Of the eight patients with severe infusion reactions, six tolerated re-infusion. Of the remaining two patients, one developed a second severe acute reaction on re-infusion, and no further attempts were made. The other patient was not retreated. Although almost every patient tolerated retreatment, prophylaxis did not always prevent further infusion reactions. This underscores the fact that in cases of severe acute infusion reactions, the risks and benefits of re-infusion need to be weighed carefully.

Because delayed infusion reactions are much less common, there are far less data available on their treatment and prophylaxis. Clinical experience suggests that these patients can be treated with acetaminophen (1,000 mg QID) and an antihistamine (either diphenhydramine 50 mg QD-BID or a second-generation antihistamine). A Medrol dose pack may be needed immediately following the infusion if there is no response to the acetaminophen and antihistamine.

Although most physicians will not re-infuse infliximab after a documented delayed reaction, we propose that it is possible. One should pre-treat with acetaminophen and either diphenylamine or a second-generation antihistamine (for 5 days prior to infusion). Type III immune reactions occur when the antigen/antibody complexes are soluble. By increasing the dose of infliximab (antigen excess), one can shift the curve to the left and decrease the formation of soluble immune complexes. In this case, one can double the dose of infliximab from 5 mg/kg to 10 mg/kg. One can also affect antigen/antibody complex formation by decreasing the interval between the infusions (which may elevate infliximab levels similarly, leading to antigen excess).

Anti-monoclonal Antibody Antibodies

The formation of antibodies to infliximab is not uncommon. The frequency in the literature varies widely, from 7–61%, but is generally 7–15% (7, 14). This broad range is at least partially attributable to the different infliximab dosing schedules used in the studies performed to date and to variations in concomitantly administered medications. It has recently been shown that formation of these antibodies to infliximab may lead to a greater risk of infusion reactions and also may limit the long-term efficacy of the drug (14–18). Several studies have demonstrated that an induction regimen followed by scheduled maintenance infusions decreases the likelihood of antibody formation (i.e., generates immunologic tolerance) (16–18). It has also been shown that the use of concomitant immunomodulators prior to starting infliximab is effective in reducing antibody production (17).

This concept of decreasing immunogenicity derives from the original trials of infliximab in RA. In the phase II trial (17) in which infliximab was given as a one-time dose, the frequency of ATI was 53%, 21%, and 7% (1, 3, 10 mg/kg) in patients receiving infliximab alone. When given in conjunction with methotrexate, the frequency of ATI was 15%, 7%, and 0% (1, 3, 10 mg/kg). Thus, concomitant administration of methotrexate and infliximab modulated the immune response to the monoclonal antibody. In the phase III trial (7), infliximab was given as an induction regimen (3 or 10 mg) at 0, 2, and 6 weeks, followed by a maintenance regimen of every 4 or 8 weeks. All patients were receiving concomitant methotrexate. Because of the maintenance regimen, most patients still had infliximab in their serum, and therefore only 60 of the 428 patients could be assessed for ATI. Of these 60 patients, only 5 (8%) were positive for ATI (if we consider indeterminate samples negative—which we do). Thus, a 3-dose induction regimen followed by maintenance infusions is less immunogenic than a one-time dose followed by episodic infusions.

In the largest study evaluating long-term infliximab for CD, the ACCENT I trial (2), patients received episodic (one dose of infliximab and then placebo) 5 mg/kg or 10 mg/kg every 8 weeks after a 0, 2, and 6-week induction regimen of infliximab. Because of the maintenance regimen, many patients still had infliximab in their serum and only 233 of 442 patients could be assessed for ATI. At week 54, 64 patients (14%) had ATI. Patients who received a 3-dose induction regimen of infliximab and then received maintenance infusions every 8 weeks were less likely to develop antibodies than were patients who received a single dose (28.1% vs. 6.3-9.1%). However, the rate of infusion reactions was the same for both groups. The rate of infusion reactions in the episodic group may have been artificially lower, however, because they received fewer infusions than the maintenance group. The frequency of ATI formation was also less in patients receiving both steroids and immunomodulators (6%) than in patients on immunomodulators alone (10%), patients on steroids alone (17%), and patients receiving neither (18%). It also appears that the 3-dose induction and maintenance regimen is slightly better than the addition of an immunomodulator for preventing antibody formation.

In a recently published study reevaluating the ACCENT I data, patients in the maintenance-scheduled treatment arm demonstrated higher remission rates and higher quality-of-life scores than did patients receiving episodic treatment. These patients also had significantly fewer CD-related hospitalizations and surgeries (18).

In the ACCENT II trial (4), 17% of evaluable patients (n=44) developed antibodies to infliximab, 31% did not (n=80), and 52% (n=134) were inconclusive for the presence of antibodies. This trial also demonstrated that patients who were on steroids (13%) or immunomodulators (11%) were less likely to develop antibodies than patients on no medications at baseline (24%). Patients who were on both steroids and immunomodulators were the least likely to develop antibodies to infliximab (4%).

Another study, by Baert et al. (14), confirmed the finding that concomitant immunomodulator therapy was associated with a lower frequency of ATI (42% vs. 75%). However, this study showed that a three-dose induction regimen without a follow-up maintenance regimen did not decrease ATI formation and was actually slightly worse than episodic treatment.

Recently, a prospective trial by Farrell et al. (15) once again confirmed that concurrent immunomodulators (odds ratio [OR] = 0.19) and a second infusion within eight weeks of the first (OR = 0.13) significantly reduced ATI formation. In the placebo-controlled portion of their trial, they were able to show that patients who were pretreated with intravenous hydrocortisone developed lower levels of ATI (1.6 microg/mL vs. 3.4 microg/mL) than did those patients who received placebo. They also demonstrated that fewer hydrocortisone-treated patients developed ATI than did those who received placebo (26% vs. 42%), although this was not statistically significant (p=0.06). Interestingly, pretreatment with hydrocortisone had no effect on the number of infusion reactions.

Response Effect of Anti-monoclonal Antibody Antibodies

Although antibodies are formed against infliximab, it is not fully confirmed that this has clinical significance. In addition to the increased risk of infusion reactions, there may be a link between antibody formation and decreased efficacy of the drug over time. In the study by Baert et al. (14), the presence of high levels of ATI (>8.0 µg/mL, an arbitrary cutoff value) prior to an infusion was predictive of a shorter duration of response (35 days vs. 71 days). These patients were also at higher risk for an infusion reaction (relative risk 2.4). Furthermore, once an infusion reaction occurred, the duration of clinical response to subsequent infusions decreased. No attempt to alter dose or interval was made in this study. The study by Farrell et al. (15) showed that patients who had ATI were more likely to lose their initial response and develop an infusion reaction. Overall, ATI were seen in 36% of their patients (19 of 53). Of the patients who lost their response to infliximab, 73% (11 of 15) were positive for ATI. This is in stark contrast to the 21 continuous responders, none of whom developed ATI. Also, all seven of their patients with serious infusion reactions had ATI. This was not the case in ACCENT I, in which there was no correlation between antibody level and increased likelihood of reaction.

It is interesting to note that in the ACCENT I and ACCENT II trials, the presence of ATI did not affect outcome at one year in patients receiving maintenance dose infusions. Of the patients who lost response on a 5 mg/kg maintenance regimen, increasing the dose to 10 mg/kg re-established response in 90%. Likewise, in those patients on 10 mg/kg who lost response, 80% regained response when increased to 15 mg/kg. (18)

Summary

The new biologic therapies have revolutionized the treatment of a number of immune-mediated inflammatory diseases. However, their immunogenicity, through the development of antibodies to the monoclonal antibody, appears to be associated with an increased risk of infusion reactions and may reduce the long-term response to these new medications. One can decrease the risk of antibody development by: (a) using concurrent immunomodulator therapy, (b) using an induction regimen followed by maintenance infusions, (c) considering steroid premedication in those patients not currently on immunomodulators, or (d) increasing the dose or shortening the infusion interval of infliximab. Once present, the immunogenicity can be overcome, at least temporarily, by increasing the dose of infliximab or shortening the dosing interval. If infusion reactions do occur, and they do in only about 5–10% of infusions, they can easily be managed as outlined above.

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The Metabolic Syndrome and Cardiovascular Disease

JAMES A. VITARIUS, M.D., PH.D.

Abstract

The metabolic syndrome, a group of conditions including obesity, hypertension, insulin resistance and dyslipidemia, is an important target in coronary heart disease (CHD) risk reduction. Many questions regarding CHD risk and pathophysiology, and optimal treatment of metabolic syndrome have been debated in recent years. These conditions individually increase CHD risk, and several lines of evidence suggest that the components, acting together synergistically, additionally raise an individual's risk of developing cardiovascular disease. Many think that insulin resistance is the key component linking the syndrome to the development of CHD from a pathophysiologic point of view; however, a chronic inflammatory state has also been implicated. New medications, such as the cannabinoid antagonists, are being tested as potential treatments for metabolic syndrome. How best to treat advanced coronary disease in patients with metabolic syndrome remains a major challenge.

Key Words: Metabolic syndrome X, cardiovascular diseases, pathophysiology, atherosclerosis.

SINCE 2001, RESEARCHERS have focused increasingly on the metabolic syndrome and its relationship to cardiovascular disease. In that year, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III identified the syndrome as a secondary target (after low density lipoprotein cholesterol lowering) of coronary heart disease risk reduction. Many questions regarding cardiovascular risk and pathophysiology, and optimal treatment of metabolic syndrome have been debated in recent years. For example: Should metabolic syndrome be regarded as a coronary risk equivalent, or does the syndrome place an individual in the intermediate risk category? Does having the syndrome impart a risk above and beyond the risks of its components? Is insulin resistance the common pathway linking the components to heightened risk for the development of cardiovascular disease? And finally, what is the best way to treat advanced ischemic heart disease in these patients?

Historical Perspective

The syndrome was probably first identified in 1923, when Kylin noted that hypertension, hyperglycemia and gout tend to cluster together (1, 2). The more modern definition, one that includes obesity, hypertension, diabetes, and hyperlipidemia, was first suggested in the 1960s. German researchers of the 1970s (e.g., Haller et al.) are credited with the first use of the term "metabolic syndrome"; they also explored the syndrome's association with atherosclerosis (3). In the early 1990s, Ferrannini et al. and Reaven suggested that the underlying cause of this syndrome was insulin resistance. Because of this, Ferrannini et al. favored the term "insulin resistance syndrome," while Reaven called it "Syndrome X" (1, 3, 4) (not to be confused with the Syndrome X exhibited by angina and a normal angiogram). ATP III used the term "metabolic syndrome" to describe the condition.

Metabolic Syndrome and Cardiovascular Risk

Using National Health and Nutrition Examination Survey (NHANES) III data, it has been estimated that 25% of the adult American population meet diagnostic criteria for metabolic syndrome

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Cardiology Fellow, The Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, The Mount Sinai Medical Center, New York, NY 10029-6574.

Address all correspondence to James A. Vitarius, M.D., Ph.D., Cardiology Fellow, Box 1030, The Mount Sinai Medical Center, One East 100th Street, New York, NY 10029-6574; email: james.vitarius@mssm.edu

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(5 – 7). This figure is in agreement with other cohorts studied (8). The percentage increases to 44% if only Americans over fifty years old are considered (3).

The two most common methods for diagnosing metabolic syndrome (Table) focus on visceral adiposity, atherogenic dyslipidemia, glucose intolerance, elevated blood pressure, and renal dysfunction (4, 9). One method gives equal importance to fasting glucose levels, waist circumference, high-density lipoprotein (HDL) levels, triglycerides and blood pressure; it was adopted by the NCEP for its ATP III guidelines. The other method, from the World Health Organization (WHO), is favored by some because it requires measurement of insulin resistance for the diagnosis.

A recent analysis of the San Antonio Heart Study (SAHS) by Hunt et al. (8) looked at all-cause and cardiovascular mortality, using either the NCEP or WHO diagnostic criteria. The SAHS followed over 5,000 patients enrolled between 1979 and 1988 in the San Antonio, Texas area over an average period of 12.7 years. Hunt et al. determined that the NCEP diagnostic criteria predicted all-cause and cardiovascular mortality, while the WHO criteria predicted cardiovascular mortality, but not mortality due to all causes. This finding was in contrast to the Finnish Kuopio Ischemic Heart Disease Risk Factor study, which concluded that of the two diagnostic methods, only the WHO criteria were associated with increased all-cause and cardiovascular mortality (8, 10).

The relationship of metabolic syndrome to cardiovascular risk can be approached in two ways: (a) by considering the individual risks posed by the components, and (b) by considering the components together as a syndrome (7, 11). Insulin resistance is thought by many to be the common pathology linking the components (1, 3, 4, 9), so a lot of attention has focused on glucose homeostasis and its role in the development of cardiovascular disease.

For example, in the mid-1970s, the Helsinki Policeman Study followed nearly 1,000 men without coronary artery disease for a period of $9^{1}/_{2}$ years and found that plasma insulin levels (as a surrogate of insulin resistance) were associated with coronary heart disease death and non-fatal myocardial infarction (12). Ducimetiere et al. followed more than 7,000 non-diabetic men aged 43 – 54 and found a similar association between fasting plasma insulin levels and coronary heart disease endpoints (13).

The San Antonio Heart Study was one of the first studies to prospectively test the hypothesis that insulin resistance could lead to metabolic derangements that would favor the development of heart disease (14). In the first phase of the study

TABLE

Definitions of the Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel III	**World Health Organization**		
At least 3 of the following:	Hyperinsulinemia (upper quartile of normal) or fasting glucose ≥ 110 mg/dL and at least 2 of the following:		
	Hyperinsulinemia ≥ 75th percentile	or	insulin resistance (Insulin clamp)
Fasting glucose ≥ 110 mg/dL	Fasting glucose ≥ 110 mg/dL	or	OGTT-2-hour glucose ≥ 140 mg/dL
Waist ≥ 102 cm for men ≥ 88 cm for women	Waist:Hip ≥ 0.90 for men ≥ 0.88 for women	or	BMI ≥ 30 kg/m^2
Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg/dL	or	HDL-cholesterol < 35 for men < 39 for women
HDL cholesterol ≤ 40 mg/dL in men ≤50 mg/dL in women			
Blood pressure ≥ 130/80 mm Hg	Blood pressure ≥ 140/90 mm Hg		
	Microalbuminuria ≥ 20 mg/min	or	Urine albumin: Creatinine ≥ 30 mg/g

OGTT=oral glucose tolerance test, BMI=body mass index, HDL=high density lipoprotein. Reprinted from Natali A, Ferrannini E. Hypertension, insulin resistance, and the metabolic syndrome. Endocrinol Metab Clin North Am 2004; 33:417 – 429 (9) with permission from Elsevier.

(beginning in 1979), approximately 1,100 Mexican and non-Hispanic white Americans were followed for an average of eight years. Individuals with the highest fasting insulin levels at the onset developed diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol at significantly higher rates (15). The relationship between fasting insulin and these conditions persisted after controlling for age, ethnicity, gender, or body mass index (BMI).

Another well-controlled study looking at insulin levels and cardiovascular disease risk was the Quebec Cardiovascular Study (16). A cohort of more than 2,000 men, recruited from the Quebec City, Canada, area, were followed for 12 years. Higher levels of plasma insulin were associated with increased risk of cardiovascular disease, even after controlling for blood pressure, medication use, family history, age, BMI, tobacco and alcohol use, and plasma lipid and lipoprotein levels.

The ongoing EGIR-RISC (European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease) is following 1,500 healthy males and females aged 30–60 years over a period of 10 years (14). In this study, insulin sensitivity is being measured by euglycemic insulin clamp, and the primary endpoint is carotid artery intima-medial thickness, determined by ultrasound. Secondary endpoints include other cardiovascular disease markers such as ECG changes, ankle:brachial pressure ratio, symptoms and events, as well as the development of diabetes, dyslipidemia, and hypertension.

Several lines of evidence suggest that the components of metabolic syndrome, acting together synergistically, raise an individual's risk of developing cardiovascular disease. Data from the Framingham Heart Study have suggested that metabolic syndrome confers a 10-year risk of 10–20% for developing cardiovascular disease (4). However, as noted by the report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to the definition of metabolic syndrome (4), statistical analysis using several models have determined that adding metabolic syndrome risk factors not already accounted for by the traditional Framingham cardiovascular risk assessment did not add to its predictive value.

The Botnia Study from Finland and Sweden studied approximately 4,500 individuals, starting in 1990, in an attempt to identify "early metabolic defects in families with type 2 diabetes" (1). Patients were divided into groups with normal glucose tolerance, abnormal glucose tolerance, and frank diabetes. The Botnia researchers found that in all groups combined, a history of coronary heart disease (angina, nitroglycerin use, or previous myocardial infarction) and stroke were more common in individuals with metabolic syndrome (defined by WHO criteria) than in those without metabolic syndrome (RR 2.96 and 2.27, respectively). Additionally, coronary heart disease risk was elevated in individuals with metabolic syndrome and normal glucose tolerance (RR 1.73). Both total mortality and cardiovascular mortality were higher in subjects with metabolic syndrome.

Alexander et al. set out to examine the increased prevalence of coronary heart disease in individuals with metabolic syndrome, by using NHANES III data for people over 50 years old. In their analysis they found that, when using univariate regression, metabolic syndrome predicted coronary heart disease prevalence with an odds ratio of 2.07. If multivariate regression was applied, metabolic syndrome was no longer a significant predictor of coronary heart disease, but blood pressure, HDL cholesterol, and diabetes were (3). A similar analysis of NHANES III data by Ninomiya et al., using multivariate statistical techniques, revealed that metabolic syndrome was associated with an increased risk of myocardial infarction and stroke (17).

Pathophysiology of Metabolic Syndrome

Understanding the pathophysiology responsible for the metabolic syndrome aids in determining the best treatment options. While the exact mechanism responsible for increased cardiovascular risk has not been elucidated, the possibilities were reviewed by Deedwania (18). He noted that insulin's action could lead to hypertension by "stimulating sympatho-adrenal axes" or by stimulating vascular smooth muscle cell hypertrophy. Insulin could also cause hypertriglyceridemia and low HDL-cholesterol through increased catecholamines. Insulin, he also pointed out, can lead to the secretion of the prothrombotic plasminogen activator inhibitor-1. Other prothrombotic conditions in metabolic syndrome include increased serum fibrinogen, von Willebrand factor, factor VII, and thrombin, as well as increased platelet aggregation (19).

Vascular endothelial dysfunction is thought to play a key role in atherogenesis. While type II diabetes is known to be associated with endothelial dysfunction, only recently has there been evidence that endothelial dysfunction also takes place in insulin resistance states without diabetes (20, 21). The reasons for this have not been worked out yet, but one possibility could be related to angiotensin II, which shares a common signaling pathway with insulin (20). It is thought that a hyperinsulinemic state may lead to increased sensitivity to angiotensin II, which in turn could cause increases in cell growth, plasminogen activator inhibitor-1, intracellular adhesion molecule-1 and monocyte chemoattractant protein-1. Defects in insulin sensitivity may interfere with insulin-stimulated endothelial vasodilation. This may occur through defects in the phosphatidylinositol 3-kinase pathway, which normally stimulates endothelial nitric-oxide synthase to produce the vasodilator nitric oxide.

The excess adiposity associated with metabolic syndrome may also play an important pathophysiologic role in the development of cardiovascular disease. The impact of obesity's role in metabolic syndrome was recently reviewed by Grundy (11), who noted that "obesity is associated with all the risk factors of the metabolic syndrome." Adiposity, especially visceral, can lead to increased free fatty acid formation from lipolysis, which has been shown to decrease insulin sensitivity by interfering with the mobilization of the glucose transporter, GLUT4 (22, 23). Other candidates for linking adiposity to insulin resistance are tumor necrosis factor-α (TNF-α), adiponectin, resistin (4, 22, 24), and leptin (25, 26).

Insulin resistance at the level of the adipocyte causes increased release of fatty acids due to a lack of glucose uptake for its use in triglyceride formation and a decreased inhibition of hormone-sensitive lipase (24). In addition to causing muscle insulin resistance and hyperinsulinemia, increased fatty acids will stimulate the liver to produce and secrete triglyceride and very-low density lipoprotein (VLDL) particles. Increased serum VLDL is "nearly always" associated with low HDL (24).

Fatty acids also serve as ligands for peroxisome proliferator-activated receptors (PPARs), which are nuclear receptors that affect gene expression. One type, PPARα, which is activated by fibrates, increases fatty acid oxidation and attenuates triglyceride synthesis and VLDL secretion. Stimulation of PPARα also leads to increased production of apolipoprotein (apo) A-I, which enhances HDL levels. PPARγ is bound by thiazolidinediones (TZDs), which stimulate the receptors and improve insulin sensitivity (24).

The role of PPARs in the development of cardiovascular disease is being investigated, but is so far unclear. For example, some data have suggested that, when activated by modified fatty acids, PPARγ may stimulate lipid accumulation in macrophages. However, activation of PPARγ has also been shown to stimulate cholesterol efflux, and TZD treatment has been shown to inhibit atheroma formation in mouse atherosclerosis models (27).

A chronic inflammatory state has been implicated in the development of atherosclerosis. Several studies have shown a link between metabolic syndrome and systemic inflammation (28, 29). For example, Festa et al., analyzed the relationship between metabolic syndrome and markers of inflammation, including C-reactive protein (CRP), in the Insulin Resistance Atherosclerosis Study (IRAS) (30). Using data from approximately 1,000 nondiabetic individuals, they showed that BMI, waist circumference, and insulin sensitivity (by glucose tolerance test and fasting insulin) were associated with levels of CRP, fibrinogen and white cell count. Furthermore, the number of metabolic conditions (dyslipidemia, visceral adiposity, insulin resistance, hypertension) that subjects had was directly proportional to CRP levels.

Ridker et al. also found this to be the case in an evaluation of the Women's Health Study (WHS) (31). In an analysis of 14,719 women (those who participated in the WHS but had diabetes or a history of hormone-replacement therapy were excluded), they determined that participants with metabolic syndrome and elevated CRP levels (≥ 3 mg/L) had a greater age-adjusted relative risk for future cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures, cardiovascular death) than those with metabolic syndrome and low CRP levels. Participants with metabolic syndrome had age-adjusted incident rates for future cardiovascular events of 5.9 per 1,000 person-years if the CRP level was ≥ 3 mg/L and 3.4 per 1,000 person-years if it was lower.

Matrix metalloproteinases (MMPs) are higher in people with diabetes and coronary disease, and are thought to have a role in atherosclerotic plaque instability (32). Treatment of diabetes with TZDs leads to a reduction in serum levels of MMP-9 (33). The same study that showed this effect on MMP-9 also demonstrated a significant decline in serum CRP with TZD treatment.

Treatment Issues

The pharmacologic treatment of metabolic syndrome and its attendant cardiovascular risk has been reviewed extensively elsewhere (18, 22, 24, 34) and will not be repeated here. One pharmacologic intervention worth mentioning for its novelty is the use of rimonabant, a selective cannabinoid type 1 blocker, for obesity and metabolic syndrome. As presented at the European Society of Cardiology 2004 meeting, the results of the RIO-Europe trial, a Phase III study comparing rimonabant to placebo in the treatment of obesity over a period of two years, showed that half of those individuals diagnosed with metabolic syndrome at the beginning of treatment no longer had the diagnosis at one year. This reversal was characterized by a decrease in waist circumference, a 27% increase in HDL-cholesterol, an 11% decrease in triglycerides, and an improvement in insulin sensitivity (35).

More recently, the results of the RIO-NA (North American) trial were presented at the American Heart Association 2004 Scientific Session. This randomized, double-blind trial showed that after two years, the percentage of those randomized to rimonabant who met diagnostic criteria for metabolic syndrome was 22.4%, down from 34.8% at the study's enrollment. As with RIO-Europe, there were statistically significant reductions (compared with placebo) in waist circumference and triglycerides, and an increase in HDL cholesterol (36).

How best to treat advanced coronary disease (CAD) in patients with metabolic syndrome and diabetes remains a major challenge. Primary and secondary prevention of myocardial infarction is especially important in the diabetic patient, because diabetics have higher mortality rates than nondiabetics following myocardial infarction (37, 38).

There is a need for clinical trials focusing on the treatment of coronary artery disease in the metabolic syndrome patient, but many insights can be gained by a survey of the trials of revascularization in the diabetic patient. The well-known *post hoc* analysis of the Bypass Angioplasty Revascularization Investigation (BARI), a trial that predated the use of intracoronary stents and glycoprotein IIb/IIIa inhibitors, showed that outcomes were improved for bypass surgery as compared to angioplasty. A seven-year follow-up of the BARI study focusing on diabetic patients (39) revealed a statistically better survival rate and a decreased incidence of non-Q wave myocardial infarction for diabetics undergoing coronary artery bypass grafting (CABG). Patients randomized to angioplasty also had a much greater revascularization rate (59.7%) compared with those randomized to CABG (13.1%).

Since then, the optimal treatment of multivessel CAD in diabetics has been the subject of some controversy. The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) suggested a greater survival rate at two years for those diabetic patients treated with CABG, and an eight-year follow-up of the Emory Angioplasty versus Surgery Trial (EAST) also supported the BARI findings (40, 41). However, the Randomized Intervention Treatment of Angina (RITA) study, and the Medicine, Angioplasty, or Surgery Study (MASS-II), which included some diabetic patients, had similar prognoses for angioplasty and CABG (42–44). Analyses of other randomized and nonrandomized trials have provided conflicting results (42).

The Northern New England Cardiovascular Disease Study Group observed 2,700 diabetic patients over five years, who were similar to the population studied in BARI but were non-randomized. Roughly 45% had three-vessel CAD, and these patients had a significantly higher mortality rate (hazard ratio = 2.02) if treated initially with angioplasty as compared with CABG. Those with two-vessel CAD also had a trend towards a mortality benefit with CABG, but it was not statistically significant (42).

A subanalysis of the Arterial Revascularization Therapy Study (ARTS) trial by Abizaid et al. (45) focused on the one-year outcomes for diabetics enrolled in this study, which randomized 1,200 patients with multivessel CAD to CABG or intracoronary stenting. Of the total number of enrollees, 200 were diabetic. Diabetic patients treated with stenting had a lower event free survival rate (63%) at one year than those treated with CABG (84%), owing to a higher rate of repeat revascularization. However, rates of all-cause mortality, cerebrovascular events, and myocardial infarction were similar, although the incidences were generally small. It should also be pointed out that only 3.5% of the diabetic patients received a glycoprotein IIb/IIIa inhibitor as adjunctive therapy to stent placement (40).

The idea that advances in percutaneous intervention such as adjunctive medical therapy would lead to better outcomes for diabetics treated with stents has been challenged by the results of a subanalysis of the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) by Mathew et al. (46). Roughly 2,600 diabetics were enrolled in this trial designed to test the efficacy of tranilast in preventing stent restenosis. Mathew et al. concluded that diabetics had a higher incidence of death, myocardial infarction and target vessel revascularization, even after controlling for a number of factors including age, smoking status, history of congestive heart failure, number of diseased vessels, and lesion type. However, the use of glycoprotein IIb/IIIa inhibitors in PRESTO was still relatively low (43%) compared to current practice.

An attempt to determine the best revascularization method for diabetics with multivessel CAD will be made by the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial (47). FREEDOM is a multicenter, prospective trial that will randomize individuals with diabetes and multivessel CAD to either CABG or percutaneous coronary intervention with sirolimus-eluting stent. Follow-up of the primary endpoint of mortality will continue for five years.

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Grand Rounds

Mechanism and Therapy of Cardiac Arrhythmias in Adults with Congenital Heart Disease

STEVEN K. FURER, M.D., J. ANTHONY GOMES, M.D., BARRY LOVE, M.D., AND DAVENDRA MEHTA, M.D., PH.D.

Abstract

Over the past few decades, surgical advances have helped to prolong the lives of many young patients with congenital heart disease (CHD). However, as these patients reach adulthood, they are at risk for many late sequelae of their disease or of their corrective surgery. One of the unique challenges associated with CHD is the high incidence of cardiac arrhythmias that arise from the myocardial substrate created by abnormal pressure/volume changes, septal patches, and suture lines. Medical therapy has proven to be disappointing in treating a majority of these cases. Nonetheless, radiofrequency catheter ablation (RFA), an effective tool in treating atrial and ventricular arrhythmias in structurally normal hearts, has been used to treat arrhythmias in adults with congenital heart disease. This review will discuss some of the common congenital heart diseases in adults and the arrhythmias associated with them, as well as the therapeutic modalities used to treat them. Finally, it will present Mount Sinai Hospital's experience in using RFA for the management of cardiac arrhythmias in adults with congenital heart disease.

Key Words: Congenital heart disease, radiofrequency ablation, arrhythmia.

Introduction

AN INCREASING NUMBER OF PATIENTS with congenital heart disease are reaching adulthood, due to the success of corrective surgical procedures. But one of the problems associated with longer survival is cardiac rhythm disturbances. The high incidence of cardiac arrhythmias in the adult with congenital heart disease (Table 1) is a result of the irritable foci caused by abnormal pressure/volume changes, and reentrant circuits created by septal patches and suture lines that are characteristic of this population.

Intracardiac shunting, leading to chronic volume and pressure overload, varying degrees of pulmonary hypertension, and ventricular dysfunction all contribute to arrhythmogenesis. In response to atrial volume or pressure overload, atrial stretch prolongs atrial refractoriness, making the atria vulnerable to the induction of atrial flutter and atrial fibrillation.

Atrial flutter is usually caused by a reentrant circuit. The circuit revolves around one or more electrical barriers such as the tricuspid valve or an atrial suture line. Injured or scarred atrial tissue from surgical incisions, such as an atriotomy site or an atrial septal defect (ASD) patch repair, creates zones of slow conduction that allow the circuit to propagate. Atrial premature beats lead to the initiation of reentry (atrial flutter) by further slowing impulse conduction in damaged tissues around area of blockage.

Ventricular tachycardia (VT) is seen in a smaller number of patients, most notably in those with tetralogy of Fallot (TOF). Progressive myocardial fibrosis of the right ventricle, with corresponding slowing of conduction, increases the incidence of reentrant ventricular arrhythmias. The surgical procedure for a right ventriculotomy scar and ventricular septal defect (VSD) patch repair also contributes to the arrhythmia substrate. The VSD patch repair provides a fixed anatomic obstacle around which reentrant arrhythmias may occur. In addition, isolated muscle bundles surrounded by fibrosis in the margin of the junction between the right ventricular outflow tract patch-right ventricular free wall will slow conduction and further con-

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From the Division of Cardiac Electrophysiology, Cardiovascular Institute, Mount Sinai Hospital and Medical School, New York, NY.

Address all correspondence to Davendra Mehta, M.D., Ph.D., F.A.C.C., Director, Electrophysiology Section and Cardiac Arrhythmia Service, Cardiovascular Institute, Box 1054, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029; e-mail: Davendra.Mehta@mssm.edu

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TABLE 1

Congenital Heart Defects and Their Associated Arrhythmias

Atrial Septal Defect
- Atrial flutter
- Atrial fibrillation

Ebstein's Anomaly
- Accessory pathways
- Atrial flutter
- Atrial fibrillation
- Ventricular tachycardia

Fontan Patients
- Atrial flutter

Tetralogy of Fallot
- Ventricular tachycardia
- Atrial flutter
- Atrial fibrillation

Transposition of the Great Arteries
- Atrial flutter
- Atrial tachycardia
- Atrioventricular nodal reentrant tachycardia
- Ventricular tachycardia

tribute to the initiation of reentry. Right ventricular dilatation and stretch with slowed ventricular activation contribute to the creation of reentrant circuits within the right ventricle, whereas impaired hemodynamics, predominantly right ventricular dilatation due to pulmonary regurgitation, are responsible for sustaining VT, once initiated.

Atrial Septal Defect

Atrial arrhythmias, primarily atrial flutter and atrial fibrillation, are the most frequently seen arrhythmias in an adult patient with an ASD. Age at surgical repair is an important predictor of persistent or new arrhythmias after ASD closure. While ASD closure often leads to improved functional status and reduces the risk of right-sided heart failure and progressive pulmonary hypertension, it is not curative or totally preventative for arrhythmias. Older age at surgery, the presence of preoperative atrial flutter or atrial fibrillation, and the presence of postoperative atrial flutter, atrial fibrillation or junctional rhythm, are predictive of late postoperative atrial flutter or atrial fibrillation (1). Several years after surgical closure, 60% of patients in one study continued to have atrial flutter or atrial fibrillation, particularly those older than 40 years of age (1). This data suggests that early closure of an ASD reduces the long-term occurrence of atrial arrhythmias.

Atrial flutter is right sided and caused by a reentrant circuit usually found around the tricuspid ring or the atriotomy scar. Catheter ablation of the area of slow conduction is the treatment of choice. Delivered from the tip of a catheter to the endocardial surface, radiofrequency energy produces controlled focal tissue ablation. Recent data on entrainment mapping (Fig. 1) combined with three-dimensional electro-anatomic mapping showed 81% successful ablation of macro-reentrant circuits in adult congenital heart disease patients, half of whom had an ASD repair (2). In older patients with atrial fibrillation, the standard maze procedure has been performed at the time of ASD closure with excellent results and no recurrence of atrial fibrillation (3). (The maze procedure employs several small incisions in the right and left atria to interrupt the potential reentrant pathways required for atrial fibrillation maintenance.)

Ebstein's Anomaly

This condition involves the apical displacement of one or more tricuspid valve leaflets from the atrioventricular (AV) ring into the right ventricle, associated with a diminution in size of the functioning right ventricle. The deformity and displacement of the tricuspid valve can result in severe tricuspid insufficiency and right atrial dilatation. These abnormalities, along with the frequent coexistence of an ASD, predispose to the development of atrial arrhythmias. In addition, there is a high prevalence of accessory pathways, usually located on the right side or in the posteroseptal region. This is presumed to be a consequence of the discontinuity of the central fibrous body and septal AV ring,

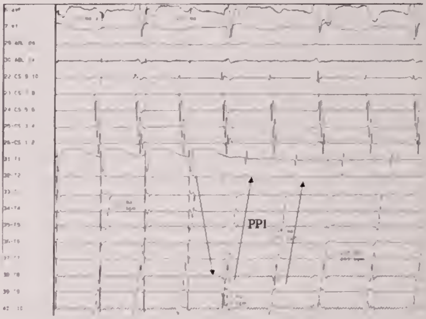

Fig. 1. Intracardiac electrograms showing entrainment mapping during scar-related atrial flutter in a patient with an ASD repair. Arrows indicate activation sequence. Top 2 channels show surface EKGs. CS channels represent recordings from the coronary sinus, 1, 2 being distal and 9, 10 proximal electrograms. T1 – 10 represent recordings from multipolar catheter placed around the tricuspid ring, T1 near the inferior vena cava and T10 in the upper septal region of the right atrium. Activation sequence is counterclockwise going from T10 to T1. Tachycardia cycle length was 295 ms. Pacing was performed at 270 ms. Post-pacing interval (PPI) was same as tachycardia cycle length (295 ms), indicating entrainment. This confirms that pacing was performed in the tachycardia reentry circuit.

resulting in persistence of fetal accessory AV pathways. Accessory pathway variants, such as Mahaim fibers, are more common in this condition.

About one third of patients with Ebstein's anomaly have an arrhythmia, most commonly atrioventricular reentrant tachycardia or Wolff-Parkinson-White, and to a lesser extent, atrial tachycardia, atrial flutter, atrial fibrillation, and VT. Atrial arrhythmias are encountered with increased frequency, with increasing age and duration of follow-up.

Radiofrequency ablation (RFA) is used to treat atrial flutter, incisional atrial tachycardia and accessory pathway conduction in patients with Ebstein's anomaly, with a success rate of 76% (4), compared to 95% of patients without the anomaly. Factors that contribute to decreased success include the complex geometry of the accessory pathway, location of the pathway along the atrialized portion of the right ventricle, abnormal endocardial activation potentials confounding identification of the accessory pathway, distorted anatomy of the AV ring, and the presence of multiple pathways. In addition to a low success rate, RFA in Ebstein's anomaly is associated with a 25% risk of recurrence (4).

Refractory arrhythmias are an indication for surgical repair. For patients undergoing tricuspid valve repair or replacement, therapeutic options include surgical cryoablation, as well as concomitant right atrial maze for chronic atrial flutter or biatrial maze for atrial fibrillation. Surgical intervention for accessory pathway-mediated tachycardia and atrioventricular node reentrant tachycardia (AVNRT) has had excellent results, without recurrence from these arrhythmias (5). In contrast, surgical intervention for atrial fibrillation/atrial flutter is less effective, with a recurrence rate of 40% (5).

The Fontan Operation

The Fontan operation is a palliative surgical procedure used for tricuspid atresia, pulmonary atresia, complex single ventricle and double-inlet ventricle. Older variants of the procedure such as the right atrium-pulmonary artery connection, have given way to newer modifications such as the lateral tunnel and external conduit, which reduce the distention of the right atrium. In response to chronic stretching secondary to persistent pressure overload, the fontan right atrium remodels and dilates. This occurs in parallel to the change in electrophysiological properties manifested by the atrial conduction delay and the imbalance of the conduction heterogeneity.

Risk factors for early postoperative arrhythmias (Table 2) include preoperative AV valve regurgitation and an abnormal AV valve (6). Older age at operation is also a risk factor, because these patients will have experienced long periods of hypoxia, volume overload, resultant ventricular hypertrophy and abnormalities of diastolic filling prior to surgery. Risk factors for late atrial arrhythmias include poor preoperative functional status, previous atrial septectomy, preoperative atrial tachyarrhythmias, older age at operation, need for AV valve replacement, pulmonary artery reconstruction, atriopulmonary anastomosis, early postoperative atrial tachyarrhythmias, postoperative sinus node dysfunction, and length of follow-up (7, 8).

Atrial arrhythmias develop in 41–61% (9, 10) of Fontan patients. The median time from fontan operation to the first arrhythmia is 7 years, with 50% having recurrent arrhythmia despite treatment (11). Fontan patients with arrhythmias have been shown to have longer P-wave duration and greater P-wave dispersion than those who do not have arrhythmias (10). Patients who develop atrial arrhythmias are more likely to develop heart failure, right atrial thrombus, left atrial enlargement, right atrial enlargement, and moderate-severe systemic valve regurgitation. But there is no difference in survival time (9). Sustained atrial arrhythmias may present with hemodynamic compromise in patients with atrial flutter and 1:1 or 2:1 AV conduction. Slowed atrial conduction results in slower flutter rates, with P wave morphology reflecting the location of reentry.

Sinus node dysfunction is common, occurring either as a consequence of the operation or due to compromise of sinus node blood supply, and is associated with the development of atrial arrhythmias. Approximately 10–15% of patients will exhibit sinus bradycardia and/or junctional escape rhythm on follow-up.

Management of the resulting atrial arrhythmias generally entails a combination of antiarrhythmic drugs, pacemakers, RFA, and reoperation. Antiarrhythmic drugs must be used cautiously, as many of these patients have underlying sinus node disease. Further, the slowing of the atrial rate facilitates 1:1 conduction during atrial reentry. Finally, proarrhythmia in a patient with ventricular dysfunction is a concern.

TABLE 2
Risk Factors for Arrhythmias in Patients Who Underwent the Fontan Operation

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Preoperative AV valve regurgitation
Older age at operation
Poor preoperative functional status
Previous atrial septectomy
Preoperative atrial tachyarrhythmias
Pulmonary artery reconstruction
Atriopulmonary anastomosis
Early postoperative atrial tachyarrhythmias
Postoperative sinus node dysfunction
Length of follow-up

AV = atrioventricular

Pacing may be required for sinus node disease and/or AV block. Due to anatomic constraints, atrial and ventricular leads have to be placed via an epicardial approach. Antitachycardia pacing has been combined with medical therapy with some success. Atrial rate-responsive pacemakers are preferred, as there is a high incidence of sinus node dysfunction. Rapid pacing prevents bradycardia and atrial extrasystoles, and may eliminate initiation of reentrant tachycardias.

RFA is associated with an immediate success rate of 83% but an at-least 20% incidence of recurrent tachycardia at short-term follow-up (12). Potential causes of recurrence include persistently abnormal hemodynamics, massive right atrial dilatation with distorted anatomic landmarks, stasis related to low flow, resulting in poor catheter tissue contact, and the inability to create deep lesions in these markedly thickened and fibrotic atrial walls. More common ablation sites often include the region of the fontan anastamosis, the lateral right atrial wall and the inferior right atrium.

Refractory atrial arrhythmias are an indication for reoperation. Surgical conversion from an atriopulmonary anastamosis to a total cavopulmonary anastomosis, along with electrophysiologically guided cryoablation, has shown excellent results in preventing recurrent arrhythmias and reducing symptoms. In a study by Deal et al., surgical cryoablation and antitachycardia pacing resulted in 83% of patients being arrhythmia-free without medications (13). Cryoablation is predominantly targeted at three locations: the inferomedial right atrium between the inferior vena cava os and coronary sinus, the superior rim of the ASD patch, and along the lateral right atrial wall corresponding to the length of the crista terminalis. For patients with atrial flutter, cryoablation is employed as part of the modified right-sided maze procedure, along with excision of the right atrial appendage and placement of an atrial pacemaker. In patients with atrial fibrillation, the maze-Cox III procedure combines the lesions of the right-sided maze with cryoablation from the pulmonary veins towards the posterior mitral or tricuspid valve annulus, and from the isolated pulmonary veins to the edge of the excised left atrial appendage.

Tetralogy of Fallot

This condition consists of four features: subpulmonary infundibular stenosis, VSD, overriding aorta and right ventricular hypertrophy. Patients with this condition are predisposed to both ventricular and atrial arrhythmias. Sustained VT has a prevalence of 4 – 7% (14) and is usually a right ventricular outflow tract reentrant tachycardia with left bundle branch morphology. Nonsustained ventricular arrhythmias are present in up to 60% of Holter readings, but recent studies have demonstrated no predictive value for subsequent sustained VT or sudden cardiac death (SCD) (15).

There is a small but persistent risk of late SCD for patients with tetralogy of Fallot (TOF), with an estimated incidence rate of 0.5 – 6% (15 – 17). Initially thought to be due to conduction abnormalities and asystole, ventricular arrhythmias are now thought to be the primary cause. Older age at initial repair, moderate or severe pulmonary regurgitation, a history of sustained VT, moderate or severe left ventricular dysfunction, a QRS duration of 180 ms or more, and a rapid increase in QRS duration are predictive of risk for sudden cardiac death (Table 3) (15). The combination of moderate or severe left ventricular systolic dysfunction and QRS duration greater than 180 ms has a positive predictive value of 66% and negative predictive value of 93% for sudden cardiac death (18). QRS duration greater than 180 ms has been shown to have 100% sensitivity and 95% specificity (19) for sustained VT and SCD in tetralogy patients. QRS prolongation reflects initial damage to the right bundle branch during tetralogy repair and late progressive QRS prolongation, secondary to RV dilatation, invariably is the result of chronic pulmonary regurgitation. Moderate-to-severe pulmonary regurgitation and aneurysmal dilatation of the outflow tract are observed with greater frequency in patients with sustained VT (14). In addition to the above findings, electrophysiology study (EPS) is used to risk-stratify these patients further, as patients with inducible arrhythmias are probably at the highest risk.

The morbidity of TOF patients is also influenced by the presence of atrial arrhythmias. One third of TOF patients manifest atrial arrhythmias (Fig. 2; 20), with congestive heart failure and recurrence of atrial arrhythmia observed on follow-up. Risk factors include older age at operation, increased atrial size, tricuspid or pulmonary regurgitation and ventricular dysfunction. Atrial flutter and atrial fibrillation were more common in patients who had long-lasting pulmonary artery shunts, early operations for residual hemodynamic lesions, older age at repair, and mod-

TABLE 3

Risk Factors for Sudden Cardiac Death in Patients with Tetralogy of Fallot

Older age at initial repair
Moderate or severe pulmonary regurgitation
History of sustained ventricular tachycardia
Moderate or severe left ventricular dysfunction
QRS duration of 180 ms or more
Rapid increase in QRS duration

erate-to-severe tricuspid regurgitation (15). Tricuspid regurgitation leads to right atrial dilatation from volume or pressure overload, and prolongs atrial refractoriness, thus creating a substrate for atrial arrhythmogenesis. These patients usually present with palpitations and less often with syncope or presyncope. Atrial flutter with 1:1 AV conduction has been postulated as a cause of SCD. Sinus node dysfunction has been reported at 36% (20).

RFA has been successfully employed for atrial flutter (Fig. 3) and VT. A large area of low voltage, consistent with scarring, can usually be identified along the free wall of the right atrium, and successful ablation can be accomplished by creating a line between the lower margin of the scar and the inferior vena cava. Prerequisites for VT ablation include inducibility on EPS, hemodynamic stability during the tachycardia to enable adequate mapping, and monomorphic morphology. VT has been localized to the right ventricular outflow tract and the infundibulotomy scar or the septal surface of the VSD patch repair, with a high immediate success rate and low rate of recurrence.

Surgical reoperation to correct the hemodynamic substrate has been attempted. A significant reduction in preexisting VT and QRS duration stabilization has been reported following valve replacement for severe pulmonary regurgitation, while concomitant intraoperative electrophysiological-guided cryoablation prevents recurrence of preexisting tachyarrhythmias (21). For patients with atrial tachycardia requiring reoperation, a modified maze procedure should be considered. Patients with VT who cannot be ablated are treated with an implantable cardioverter defibrillator (ICD).

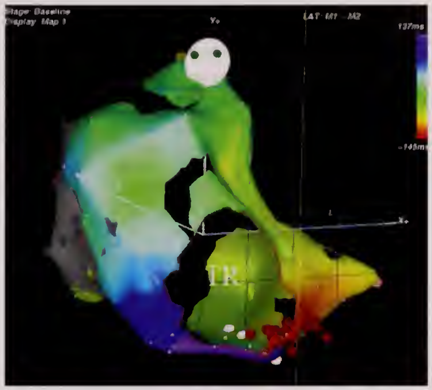

Fig. 3. Electroanatomic map of right atrium during atrial flutter in a patient with tetralogy of Fallot. Activation sequence is color-coded. Red areas represent early activation and purple areas late activation. This image depicts counterclockwise activation around the tricuspid ring (TR). Red spots represent areas of catheter ablation that lead to termination of atrial flutter. Gray areas represent areas with scarring with no electrogram. Reentry was not related to the scar.

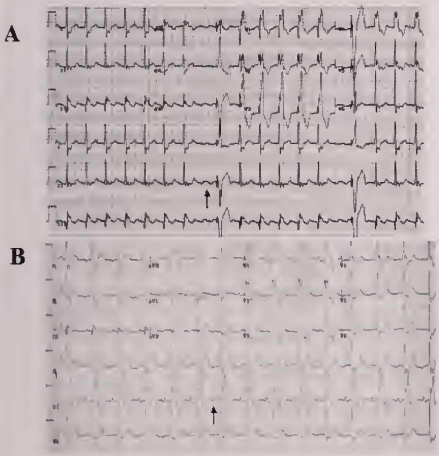

Fig. 2. Twelve-lead EKGs during 2 different tachycardias in a patient with tetralogy of Fallot. **(A)** shows p waves (arrow) suggestive of typical atrial flutter with a saw-tooth pattern in lead II. **(B)** shows a second tachycardia with p wave morphology suggestive of an atrial tachycardia. P waves are positive in lead II (arrow). This was mapped to be a focal atrial tachycardia originating from the high right atrium.

Transposition of the Great Arteries

Transposition of the great arteries (TGA) occurs when the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. At birth, the patent foramen ovale and patent ductus arteriosus allow for mixing of blood to sustain life. The Mustard and Senning operations were developed to correct the physiologic abnormality by forming a baffle within the atria to switch the flow of blood at the inflow level. The arterial switch operation was subsequently created to enable the left ventricle to become the systemic ventricle. The Mustard repair requires extensive incisions and suture lines in the atria. This results in intra-atrial conduction delays and abnormalities in atrial refractoriness, creating the substrate for atrial flutter.

In the adult Mustard patient, there is a high incidence of systemic right ventricular dysfunction associated with late atrial arrhythmias. There is also a higher risk of SCD, reported at 7% on long-term follow-up (22), attributed to ventricular arrhythmias or atrial flutter with 1:1 AV conduction degenerating to ventricular fibrillation, and asystole. Increased QT dispersion is a marker for heterogeneity of ventricular repolarization, with fast heart rates due to physical stress or atrial flutter, and ectopic ventricular beats serving as triggers to reentrant ventricular arrhythmias. Increased QT dispersion and loss of sinus rhythm have been associated with SCD.

At long-term follow-up of adult Mustard patients, only one third remained arrhythmia-free (23). A progressive loss of sinus rhythm has been observed at a rate of 2.4%/year with sinus rhythm present in 77% at 5 years and 40% at 20 years (24). The majority of supraventricular tachycardia are due to atrial flutter (23). Risk factors for supraventricular tachycardia include pulmonary hypertension, systemic ventricular dysfunction, and childhood junctional rhythm. Loss of sinus rhythm has been associated with previous septectomy, postoperative bradycardia, late atrial flutter, and preoperative arrhythmia. This loss of sinus rhythm is in contrast to the long-term maintenance of sinus rhythm in 95–98% (25) of arterial switch patients. The incidence of supraventricular tachycardia is also significantly lower, with a rate of 5% (25) in arterial switch patients, compared to 48% in Mustard patients. The arterial switch operation is likely to be associated with a lower incidence of long-term atrial arrhythmias, because there are no atrial scars.

Approximately one fifth of adult Mustard patients will require pacing in long-term follow-up for symptomatic sinus node dysfunction or atrioventricular block, or to facilitate treatment of tachyarrhythmias (23, 26). Careful evaluation of individual anatomy and exclusion of baffle leaks must be performed prior to determining pacemaker location.

Given the high prevalence of arrhythmias in this population, RFA has been employed with a 73–83% success rate (27–29), and a 12% rate of recurrence (27). The isthmus of tissue between the tricuspid valve and inferior vena cava orifice, the area of the mouth of the coronary sinus, and the region extending from the mouth to the tricuspid annulus are critical components in the reentry circuit. Intra-atrial reentry may involve either atrium and may require a retrograde aortic approach to facilitate ablation in the pulmonary venous atrium. In addition, focal atrial tachycardia has been localized adjacent to baffle suture lines, while typical AVNRT can also occur.

Sudden Cardiac Death

A large population-based study estimated the incidence of late SCD in patients with congenital heart disease who have undergone surgery to be 0.9/1,000 patient-years (30). There is an increased incidence in patients with TOF, TGA, coarctation of the aorta and aortic stenosis. The event rate for the previously mentioned group of patients with obstructive left heart lesions and cyanotic defects was found to be 2.2/1,000 patient-years compared to a rate of 0.14/1,000 patient-years in those with left-to-right intracardiac shunt lesions or pulmonic stenosis. While the most common cause of SCD is arrhythmic in origin, embolic events, aneurysm rupture, and acute ventricular failure have been reported as well.

The risk of SCD after repair of TGA starts early after repair and remains constantly high thereafter. The rate of SCD is 4% at 10 years and 9% at 20 years. In contrast, the risk of SCD after repair of TOF is less and occurs only late after repair. The risk in this group is 2.2% at 20 years, 4% at 25 years, and 6% at 30 years. Coarctation of the aorta also shows a higher risk of late SCD, 1% at 20 years, and 8% at 30 years, associated with profound left ventricular hypertrophy. Identification of patients with the highest risk, correction of hemodynamic defect, and use of ICDs will help prevent sudden death. The use of ICDs for the prevention of SCD in adults with congenital heart disease is relatively safe and effective.

Mount Sinai Data on Radiofrequency Ablation

Between 2001 and 2004, 28 EPSs were performed in 18 adult patients with surgically repaired congenital heart disease, to evaluate cardiac arrhythmias. Conventional activation mapping, electro-anatomical mapping, and entrainment mapping were performed to delineate each patient's arrhythmia. There were 13 female and 5 male patients, with a mean age of 40 (range 24–67 years) at EPS. There were 4 patients with TOF, 3 with TGA, 1 with a single ventricle treated with a Fontan operation, 1 with a VSD, 2 with Ebstein's anomaly, 2 with Ebstein's anomaly and an ASD, and 5 with an ASD. Patients were followed a mean of 22 months (range 3–44 months).

The arrhythmias documented on EPS included: 15 atrial flutters, 3 AVNRTs, 6 accessory pathways, 2 atrial tachycardias, and 2 atrial tachycardias/atrial flutters. RFA was performed on the induced arrhythmia in each patient. The overall immediate post-procedure success rate was 26/28 (93%). Six of the 18 patients (33%) had a recurrence of arrhythmia, 4 had a new arrhythmia, and 2 had an arrhythmia identical to the initial tachycardia. These data demonstrate that RFA is successful. Recurrence rates can be significant; however, the recurrent arrhythmia is often different from the one ablated and can be treated by repeat ablation procedure.

Eight patients with TOF presented with VT; all had ICD implants. These patients were followed for 6 months to 7 years. Four of the patients have had recurrent VT appropriately treated by ICD. None of these patients have died.

Conclusion

Adults with congenital heart disease often experience cardiac complications many years after surgical repair of their defect. As these patients age, cardiac arrhythmias typically cause significant morbidity. These arrhythmias are treatable with hybrid therapy involving drug therapy, catheter ablation, implantable devices, and surgical repair of the underlying hemodynamic abnormality. Appropriate treatment is associated with long-term maintenance of sinus rhythm and decreased morbidity and mortality.

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American Medical Students in 19th-Century Europe

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.P.G., F.R.C.S.

Abstract

Many Americans studied medicine in Britain in the 18th century, but the major influx to Europe began after 1815, when the French Revolution's reforms of health care and medical teaching had reached their zenith. Americans were well trained in France (and later in Germany) in medicine, surgery, pathology and clinical science, and brought these skills back to the US. Their training had been in countries with government-run, relatively egalitarian health care systems. On their return, they did not seek to transplant such a system to the US, but they did introduce European medical science and medical techniques, and something of the European medical education system.

Key Words: American medical students, Europe, Britain, France, Germany, medical schools.

THE FRENCH REVOLUTION OF 1789 led to major advances in French health care and education (1 – 11). After the Napoleonic Wars ended, in 1815, American doctors began flocking to France. I discuss earlier medical education in the US, what Americans found in Paris, and the changes they made to American health care when they returned home.

American Medical Education

The first detailed account that I have found of a 17th-century American medical education is that of George Starkey, born in 1627 in Bermuda, and soon an expert on its fauna (12, 13). He distrusted the tradition of honeybees "coming out of dead kine [cows], fermented with the falling dew," because his experiments did not produce spontaneous generation. At 16 he went to Harvard, where the curriculum was slightly different from today's. His first year included logic, physics, Greek and Hebrew, history, botany, rhetoric and divinity. In year two he studied ethics, politics, Greek, Aramaic, rhetoric and divinity. In year three he took arithmetic, geometry, astronomy, Syriac (a dialect of Aramaic) and still more rhetoric and divinity. Harvard did not teach chemistry, and this he learned from Governor John Winthrop. By age 20, he had his BA and MA and was practicing medicine as well as reading Paracelsus and van Helmont, to experiment with alchemy. He then followed both vocations in England, only to die from plague caught from a patient.

In the 18th century, Americans began going to Europe to study medicine, at first to England and Scotland, and later to France. Philadelphia was then the third largest city in the British Empire; only London and Dublin were larger. Its hospitals, such as the General Hospital of 1732 and the Pennsylvania Hospital of 1751, are almost as old as those in Britain, with the two exceptions of medieval St. Bartholomew's and St. Thomas's. Even its medical publisher, Lea and Febiger, dates back to 1785. However, there was still no medical school in the US.

John Morgan therefore sailed from Philadelphia in 1760 to study in London with the brothers John and William Hunter, and then in Edinburgh with Robert Whytt, who had himself been trained by Boerhaave in Leyden (the Netherlands). Finally, Morgan went to Padua (Italy) to learn pathology from Morgagni, before returning home to start a medical faculty at Philadelphia, aiming at world standards, just as Edinburgh had based itself on the Leyden system.

Eighteenth-century health care in Philadelphia and New York followed the British model of municipal hospitals for the indigent, together with voluntary secular charitable teaching hospitals (which also charged those who could pay). Public dispensaries coped with those not needing admission, seeing them for free either in their own homes or at the facility, as outpatients. These institutions were staffed on a voluntary basis by doctors who earned their living from their moneyed patients on a fee-per-service basis.

From the Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Dr. J.H. Baron, Division of Gastroenterology, Box 1069, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029-6574; e-mail: hughbaron@aol.com

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French Medical Education

As early as 1790, the French Revolution initiated a program of the Duke of Rochefoucauld-Liaincourt, which specified that health was a human right and "Public welfare owes the ailing poor assistance that is prompt, free, assured and complete" (4). A major stimulus was Enlightenment idealism, and the Revolutionary slogan *liberté, égalité, fraternité* derived from that idealism.

In 1790, all hospitals became properties of the state, and the old Faculty of Medicine and its medical licensing system were abolished. In 1792 the universities and medical schools were closed. Then came the anti-revolutionary wars, with heavy casualties; in particular, 900 Army medical officers were killed in battles between 1792 and 1794. In December 1794, French hospitals and universities were reorganized and teaching re-started at three old medical schools, and later at five new military medical schools, to educate medical officers for the army and navy.

Teaching was mostly in French rather than the traditional Latin, and by full-time, state-salaried professors, appointed by competition after public advertisement. They received a percentage of the students' fees and 5,000 francs per year (then about £250 or US$25, and perhaps equivalent to $20,000 today). Fees were low, at 400 francs over the four years. Students did not have to attend lectures, but they did have to pass five public exams (another 500 francs) in subjects such as hygiene and legal medicine, and write a dissertation to be defended in public. Each year there were 550 national scholarships for the three schools, 300 in Paris, 150 in Montpelier and 100 in Strasbourg. The scholarship students (*élèves de la patrie*) were paid their fees and travel expenses, and a stipend, but they were still at the poverty level, often with wooden shoes. However, student numbers increased rapidly, and by 1825 there were 2,000, that is 300 per year. These medical schools also trained pharmacists. And unlike the situation elsewhere in Europe and in the US, surgeons were given professional status equal to that of physicians.

Between 1806 and 1829, 18 provincial hospitals were recognized as secondary schools, training only pharmacists, who after eight years in practice could be appointed *officiers de santé*, the equivalent of the British apothecary as primary care physician. Paris was allotted a national school for training midwives in a totally resident 12-month program, if necessary paid for by their districts or hospitals.

A 1793 decree set up a salaried eleven-member General Board that met twice a week to advise the Minister of the Interior's salaried five-member commission to execute orders to the metropolitan central store of drugs and materia medica, as well as to the hospitals. Each hospital was run by a male and female inspector, compulsorily resident and with absolute internal authority. There were many hospitals, both specialized and general, such as the Hôtel-Dieu with 1,500–2,000 beds and not more than three patients per bed, instead of the pre-revolutionary three to six, or the target of "one-bed, one-patient" decreed by the Convention in 1793. Patients were admitted on receiving days, or by a daily decision of a central committee of two physicians and two surgeons, who could instead instruct a district charity to care for the patient at home. Every ten days the *Gazette de Santé* published numerical data of the list of registered diseases in Paris. Postgraduate positions were allotted by competitive examination, and in 1803 a national licensing system was restarted and run regionally.

In 1815 the *London Medical Repository* contrasted the French and British medical systems as follows: "There are [in France] no hospitals supported entirely by voluntary contributions: a striking contrast to what is the case in London. Indeed it is a characteristic of the two countries, that in France the government meddles in and is connected with every establishment of public utility, whereas in England it neither meddles in, nor indeed cares little about any thing of the kind." (1).

Baron Dupuytren, at the Hôtel-Dieu from 6 to 9 AM, taught on a ward round of his 200 or more patients, and then lectured, performed surgery and viewed necropsies. In the afternoon he saw outpatients (perhaps 10,000 per year), followed at 6 PM by a ward round of those he had operated on. The approximately 1,200 students who attended his lectures were not allowed to speak to him unless he spoke to them first (11).

Another surgeon at the Hôtel-Dieu gave "as much attention to minor cases as to some important cases, but he did not run through the wards as if he was thinking all the time of his patients who were expecting him abroad, and of whom he was expecting a good fee" (1). "The French physicians and surgeons display a degree of attention and zeal in the execution of their duties truly exemplary.... The public professional duties are ever the primary consideration, for which the trifling salary they receive is a pitiful remuneration: while in the London hospitals, it is too evident that public appointments are generally considered but the stepping-stones to practice and private emolument" (1).

The Hôtel-Dieu had 53,000 admissions annually, producing 24,000 corpses each year, sufficient for dissection, whether for anatomical study, for necropsy of patients the student had studied alive, or for future surgeons to practice their surgery.

Americans in France

Unlike Starkey's training at Harvard, in the 19th century almost all American medical teaching was narrowly practical. Seeking a better balance of theory and practice, thousands of American medical students came to study in Europe. At first they came to France, where the science and medicine were the best in the world, fees were minimal and living in Paris was both cheap and pleasurable. In the 1820s, 105 Americans came to study Parisian medicine, 222 in the 1830s, 128 in the 1840s and 279 in the 1850s. They returned home when they had perfected their normal and pathological anatomy and their clinical and operative skills. What did they learn, and how did their time in France affect their clinical practice in the US?

French Medicine

French medicine in the first half of the 19th century was based on three principles: physical examination (especially using Laennec's stethoscope), post mortem examination, and statistics of hospital diagnoses and results, as well as public health data. American students in Paris certainly became better clinical diagnosticians. The new teaching was clinically based; from their first day, students worked in the hospital wards and morgues. *Peu lire, beaucoup voir, beaucoup faire* was the aphorism: Read little, see much, do much. Some Americans in Paris would have learned evidence-based clinical logic from Pierre Louis's methodical case recording and statistical approach, which revealed that bleeding did not help patients and that purgatives did not help patients with gastroenteritis. Yet in spite of Louis, no pathological research on his model took root in the US, where in the absence of routine autopsies by specialist pathologists or the patients' physicians, post-mortem rates were low by European standards. Eventually didactic reading returned to French medicine. By the 1830s, 32 medical and scientific journals were being published and there were soon four great dictionaries: *Dictionnaire des Sciences Médicales* in 60 volumes (1812–1822), *Dictionnaire de Médicine* in 30 volumes (1832–1846), *Dictionnaire de Médicine et Chirurgie Practique* in 42 volumes (1829–1836) and *Dictionnaire Encyclopédique des Sciences Médicales* in 100 volumes (1864–1889). Over 300 French medical books were published in the 1830s.

In the 1830s, some American hospitals began the university-level teaching of medicine by Paris-trained doctors, who then went on to translate into English the new, authoritative French textbooks. For example, in 1832 Henry Ingersoll Bowditch helped Pierre Louis to found the *Société Médicale d'Observation*, where there was critical discussion of a patient's clinical progress and necropsy (14, 15). Returning home, Bowditch was appointed to Harvard, where in 1834 he started the (Boston) Society of Medical Observation, which met twice a week for case presentations. These were the ancestors of that great American teaching model, the clinico-pathological-conference, CPC, later regularly published verbatim in the *New England Journal of Medicine*. Only a few Americans actually absorbed French basic and clinical science, but some of those few did return home to start medical departments and laboratories.

German Medicine

Between 1834 and 1892, about 150 new American medical schools were founded, most of relatively poor quality. Few efforts were made by the French-trained physicians to establish high-quality medical schools according to the French model. But then came the critical change in American postgraduate medicine: Germany and Austria replaced France as destinations for American medical students and physicians (16). Fewer than 50 went to Germany or Austria before 1850, but between the Civil War and the First World War, nearly 15,000 went: 10,000 to Vienna, 3,000 to Berlin, 1,500 to other German-speaking universities, and 200 to Switzerland. German medicine offered *Lehrfreiheit*, freedom of teaching, and *Lernfreiheit*, freedom of learning, with salaried full-time professors, specialties and subspecialties, and in effect created medical laboratory science.

By the end of the nineteenth century, university hospitals such as Johns Hopkins in Baltimore were created, with full-time salaried professors who were also chiefs of service. The model of German clinical science and university (undergraduate and postgraduate) medical education thus had a decisive effect on the structure of American medical education.

Health Care and the Social System

There were, however, limits to the innovations that French- or German-trained American physicians either could or perhaps wished to introduce to the US, where health care was, and still is, fee-per-service and not a general entitlement. Specifically, they did not seek to redirect the American system in the direction of the government-subsidized, government-controlled systems then and now prevalent in Europe. Americans' historical reluctance to surrender too much power and control to their government was probably a major factor here. Mark Twain expressed this attitude eloquently in 1867 (17): "The mania for giving the Government power to meddle with the private affairs of cities or citizens is likely to cause endless trouble, through the rivalry of schools and creeds that are anxious to obtain official recognition, and there is great danger that our people will lose that independence of thought and action which is the cause of much of our greatness, and sink unto the helplessness of the Frenchman or German who expects his government to feed him when hungry, clothe him when naked, to prescribe when his child may be born and when he may die, and, in fine, to regulate every act of humanity from the cradle to the tomb, including the manner in which he may seek future admission to paradise."

Mark Twain's viewpoint has prevailed to at least some extent, so that the US remains the only developed country in which health care is not a universal human right and which therefore does not provide government-subsidized health care for all. Yet here too, European influence has made some headway, with the 20th century bringing some government-funded health care programs: for the indigent, the elderly, the uninsured, etc.

Free Medical Treatment in the US

There are examples in the US of free medical treatment. The Medicaid program provides free medical coverage for those with income at or below the poverty level. Prisoners receive free health care (18), even if a heart transplant is indicated (19). And patients with chronic renal failure receive free treatment, even for dialysis and transplant, since Congress passed a Social Security amendment in 1972 (20).

Conclusion

I have tried to summarize the development in France after the 1789 Revolution of a centralized national health service with government-sponsored training of doctors, nurses, midwives and pharmacists, as well as government-run university teaching. I have explained how American doctors flocked to Paris, and later to Austria and Germany, to learn from their programs, and returned home to introduce much of what they had learned at European schools and hospitals. Yet the American health care system remained primarily American, rather than European, in spirit, and a fully subsidized, government-controlled system was not imported.

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Multiple Primary Intrathoracic Neoplasms:

Case Report and a Review of the Literature

Tatjana Peroš-Golubičić, M.D., Ph.D.[1], Silvana Smojver-Ježek, M.D., M.Sc.[2], Marijan Gorečan, M.D.[3],
Njetočka Gredelj, Jasna Tekavec-Trkanjec, and Marija Alilović

Abstract

This is a case report of a patient diagnosed with three distinct primary intrathoracic tumors (mesothelioma, carcinoid and B-cell lymphoma). The patient had previously had mycosis fungoides.

The occurrence of multiple neoplasms in a single patient, synchronous or metasynchronous, is not a rare phenomenon; the incidence varies from 1 – 11% of all neoplasms. They can be hereditary, or connected with some environmental agents or previous therapies. The incidence of multiple neoplasms increases with age. We report an extremely rare case of multiple intrathoracic neoplasms in a 71-year-old man. A left upper lobectomy was performed, followed by 6 courses of chemotherapy and irradiation of the sternum. The patient was stable two years later.

Key Words: Intrathoracic, multiple neoplasms.

Introduction

MULTIPLE PRIMARY NEOPLASMS in a single patient were reported as early as the end of the 19th century (1). The pathologic criteria of multiple neoplasms were summarized by Warren and Gates (2): tumors are considered to have arisen independently if they exhibit different histological characteristics indicative of a subtype or degree of differentiation, or if they are located in different lobes and are not accompanied by tumors of other organs (2). Molecular markers, including the pattern of DNA ploidy, chromosome 3p depletion, K-ras and p53 mutational pattern, have also been used to identify the independent origin of multiple tumors (3).

Multiple neoplasms could be defined by when they appear, as synchronous or metasynchronous; the latter are defined as appearing 6 months or more following the first neoplasm (4).

The etiopathogenesis of multiple neoplasms (5) includes hereditary aspects (familial occurrence with increased incidence as well as the influence of the "protective" factors) (6, 7). It also includes the influence of external factors (tobacco, combined effects of tobacco and alcohol, asbestos, nutritional factors, viruses, the loss of immunity) (8 – 10); the effects of previous therapies (especially with cytotoxic agents and hormones, immunosuppressants and irradiation) (11, 12); and the influence of tumor-producing hormones (secretin, gastrin, bombesin, cholecystokinin, vasoactive intestinal peptide) (13; Table 1). From a review of the recent literature it would appear that the incidence of multiple neoplasms increases with age (14).

Case Report

A 71-year-old man was admitted to the hospital with a one-month history of chest pain, dry cough, dyspnea and malaise. He was a retired clerk who had never smoked. For twenty years, he had lived in a large city, close to a major highway. Five years earlier, he had been treated for biopsy-proven mycosis fungoides with etretinate for six months, with considerable success. Chest auscultation showed diminished breath sounds in the left

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From the Departments of [1]Pneumology, [2]Cytology, and [3]Radiology, University Clinic for Lung Diseases "Jordanovac," 10 000 Zagreb, Jordanovac 104, Croatia.

Address all correspondence to Tatjana Peroš-Golubičić, M.D., Ph.D., Associate Professor, Pneumonologist, University Clinic for Lung Diseases, 10 000 Zagreb, Jordanovac 104, Croatia; e-mail: tperos-golubicic@net.hr

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TABLE 1

Some Etiopathogenic Factors of Multiple Primary Neoplasms in a Single Patient (5)

Causative Factor	Location and/or Type of Neoplasm
Chemical	
Tobacco	Lungs, upper respiratory tract
Tobacco + alcohol	Larynx, lungs, upper digestive tract
Asbestos	Mesothelioma, lungs
Cadmium	Prostate, kidneys, lungs
Nickel	Lungs, paranasal sinuses
Arsenic	Skin, lungs
Nutritional and/or Endocrine	Breasts, corpus uteri, ovaries, colon
Viral	Burkitt's lymphoma, non-Hodgkin's lymphoma
Immunodeficiency	Thymoma, skin cancer, non-Hodgkin's lymphoma Following the therapy for Hodgkin's disease, lymphomas and Kaposi sarcomas in AIDS

lung. Routine laboratory findings were normal, except for a sedimentation rate of 130. The chest x-rays showed hyperinflation of the parenchyma in the supradiaphragmal and retrosternal regions, a pathological process of the anterior upper mediastinum, an infiltration of the peripheral lingula 3 cm in diameter and a smaller one in the apicoposterior subsegment of the left upper lobe (Figs. 1a and 1b). Fiberbronchoscopy showed a tumor with smooth surface in the subsegmental bronchus of the left upper lung lobe. Bronchial brushing cytology (Fig. 2a) and pathohistological analysis of the tumor biopsy proved that the tumor was carcinoid. Transthoracic fine-needle aspiration of the mediastinal mass did not reveal its etiology.

The patient underwent a left upper lobectomy, and mediastinal biopsy was performed. During the operation the node in the lingula was seen to be fixed to the pericardium. Intraoperative imprint cytology of the infiltrate in the lingula and pericardium revealed a malignant tumor. The tumor was firm, grayish-white, 2.5 × 2 cm in size, composed of pleomorphic, atypical epithelial cells in tubulopapillary formations, and desmoplastic stroma (Fig. 2b). The immunohistochemistry showed neuron specific enolase (NSE) and epithelial antigen (BerEP4) negative, and epithelial membrane antigen (EMA) and cytokeratin positive tumor cells. Pathohistological diagnosis was malignant mesothelioma. A similar infiltrate was found in the upper lobe of the left lung, 0.4 × 4 cm in size. In the apicoposterior subsegmental bronchus of the left upper lobe, a sharply demarcated, smooth, soft, fleshy tumor was found, 0.8 cm in diameter, composed of uniform cells with eosinophilic cytoplasms in acinar formations, NSE and cytokeratin positive, and EMA negative. The diagnosis was typical carcinoid. The mediastinal tumor was white, homogenous, 4 × 2 × 0.6 cm in size, composed of a mixture of small lymphocytes, plasma cells and plasmacytoid lymphocytes. Cells were CD19 and CD20 positive, and CD3 and CD5 negative, by immunohistochemistry. The diagnosis was B-cell non-Hodgkin's lymphoma-lymphoplasmocytoid type immunocytoma. In two of the synchronous tumors, immunocytoma and mesothelioma, overexpression of the p53 tumor suppressor gene product was found by immunohistochemistry.

Six months postoperatively, a painful tumor of the sternum arose. The chest computed tomography (CT) scan showed a mediastinal mass with ventral, thoracic border, which was not sharp but irregular, suggesting infiltrative growth (Fig. 1c). Fine-needle aspiration showed a mixture of small lymphocytes, plasma cells and plasmacytoid lymphocytes, which corresponds to previously described B-cell non-Hodgkin's lymphoma (Fig. 2c). The patient underwent six courses of chemotherapy (protocol CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone) and irradiation of the sternum. Two years later the patient was without symptoms, conventional chest x-ray and CT scan showed only a fibrous residue, and there were no signs of local or distant spreading of any of the tumors.

Discussion

This is a case report of a patient diagnosed with three distinct primary intrathoracic tumors (mesothelioma, carcinoid and B-cell lymphoma)

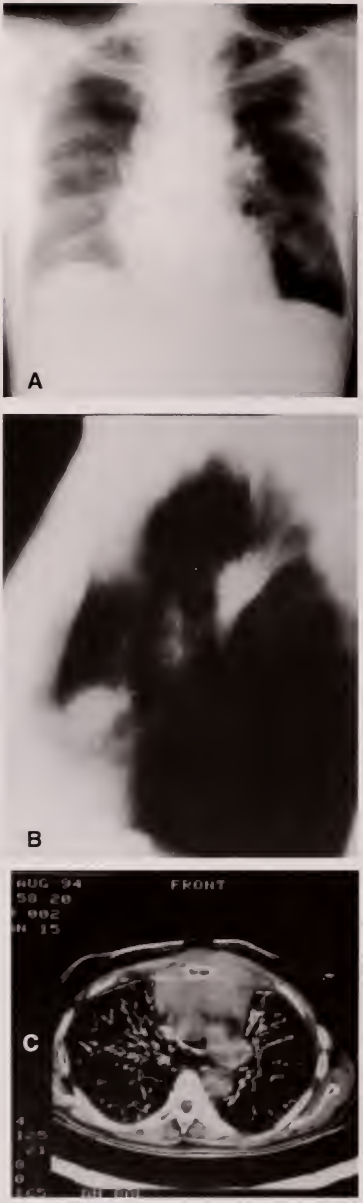

Fig. 1. Chest radiographs: (A) anteroposterior view, (B) lateral view, and (C) computerized tomography illustrating the mediastinal mass.

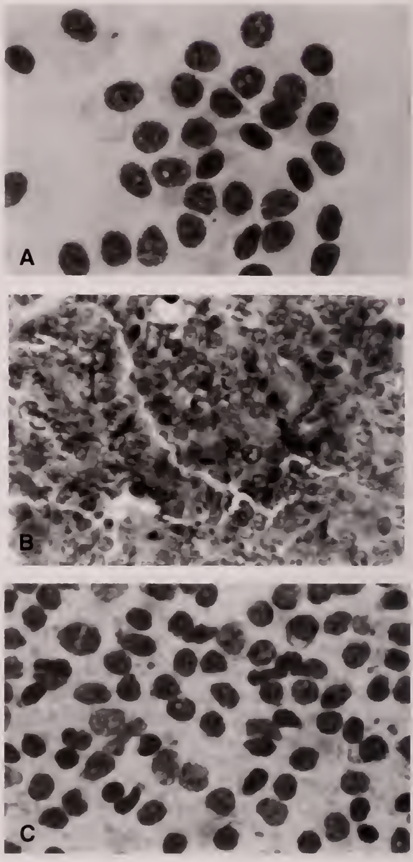

Fig. 2. Pathohistology and cytology microphotographs: (A) carcinoid imprint cytology of the tumor biopsy, (MGG, original magnification × 1000), (B) biopsy specimen of the lingula and pericardium mesothelioma (H&E, original magnification × 400), and (C) immunocytoma fine-needle aspiration cytology, (MGG, original magnification × 1000).

MGG = May-Grünwald-Giemsa stain; H&E = hematoxylin and eosin stain.

and who had previously had mycosis fungoides. Multiple primary neoplasms in a single individual are extremely rare when more then three distinct lesions are considered (15). The incidence of multiple primary lung cancer ranges from 0.5 – 10% (16).

More than 10% of patients with metachronous primary lung tumors survive longer than 3 years after the diagnosis. Criteria of multiple lung neo-

TABLE 2
Reports of Multiple Primary Malignant Neoplasms

Authors	Ref	Multiple primary neoplasms	No. of patients	Year
Efremidis	22	Lymphocytic neoplasia, Mesothelioma	2	1985
Kantor	23	Cutaneous T-cell lymphoma Cancers of lung and colon NHL	35	1989
Tondini	10	Mesothelioma, NHL-B-cell	Case report	1994
Gerstle	19	Gastrointestinal carcinoid, Malignant neoplasms of gastro-intestinal or other locations	32	1995
Takabe	20	Mesothelioma, NHL-B-cell	Case report	1997
Beshay	21	Typical pulmonary carcinoids	Case report	2003

NHL-B-cell = B-cell non-Hodgkin's lymphoma

plasms, modified from Martini and Melamed, include demonstration of tumors with different histology and proof that the tumors, if histologically similar, arise from separate and distinct endobronchial foci (17). Many authors exclude cases in which there is more than one tumor of a given histological type, arguing that the second tumor cannot be distinguished from intrapulmonary metastasis (18). The patient reported in this article had three intrathoracal malignant tumors of different origins. He had carcinoid, mesothelioma, and intrathoracic B-cell lymphoma, as well as cutaneous T-cell lymphoma (i.e., mycosis fungoides).

Some reports of patients with similar multiple, primary, malignant neoplasms are listed in Table 2 (10, 19–23).

Etretinate is a monoaromatic retinoid used in the treatment of keratinizing skin disorders and cutaneous T-cell non-Hodgkin's lymphomas (24). Teratogenic potential has been described, as well as the induction of different skeletal alterations, including periosteal osteosarcoma (25). Etretinate had been administered to our patient for 6 months, five years before the diagnosis of multiple second malignancies, and we cannot exclude a possible connection between those events.

No specific hereditary syndrome could be identified from the patient's family history. A possible environmental causative agent responsible for the development of the multiple malignancies is asbestos exposure, because our patient lived near a major highway for twenty years. A strong association between asbestos exposure and incidence of mesothelioma is well known, but there are contradictory results in studies investigating the association between exposure to asbestos and incidence of non-Hodgkin's lymphoma (26).

Several studies have shown increased risk of multiple neoplasms for older patients, especially for those treated earlier with aggressive anticancer drugs. Out of all the patients who developed multiple neoplasms, 71–94% were older than 50 years in different series (27–31). The reason for increased incidence of multiple neoplasms could be a generally older population, environmental causative agents and more effective antitumorous therapy that prolongs patients' lives and increases the risk for other primary neoplasms. Our patient, as reported, had been treated for an earlier malignancy.

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Different Glomerulopathies Accompanying Non-Small-Cell Lung Cancer

Saime Paydas, M.D.[1], Baris Soydas, M.D.[1], Semra Paydas, M.D.[1],
Mustafa Balal, M.D.[1], Seyda Erdogan, M.D.[2], and Ilhan Tuncer, M.D.[2]

Abstract

The coexistence of lung cancer and glomerular lesion is not commonly reported. Malignancy-related glomerulopathy is commonly membranous glomerulonephritis. Other glomerulopathies are seldom reported. We report two cases presenting with non-small-cell lung cancer, acute renal failure and nephrotic syndrome secondary to membranoproliferative glomerulonephritis and amyloidosis.

Key Words: Lung cancer, malignancy, glomerulopathy, proteinuria.

NEOPLASM-RELATED NEPHROTIC SYNDROME has been recognized for years. Nephrotic syndrome is rare in the course of carcinomas. Lymphoproliferative diseases are the most common neoplasms accompanying nephrotic syndrome (1). The renal lesion of paraneoplastic nephrotic syndrome usually presents as membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), minimal change disease, focal segmental glomerulosclerosis and the other glomerulopathies (2). Coexistence of lung cancer and glomerular lesion is not commonly reported. We report two cases presenting with non-small-cell lung cancer, acute renal failure and nephrotic syndrome secondary to membranoproliferative glomerulonephritis and amyloidosis.

Case 1

A 48-year-old-man was admitted to our hospital with cough, purulent sputum, dyspnea and lower extremity edema of one-month duration. He had a 60-pack/year smoking history. Physical examination on admission revealed a temperature of 37.5°C, pulse rate of 92/min, respiratory rate of 25/min, and blood pressure of 150/90 mm Hg. Other significant physical findings were the absence of respiratory sound in middle and upper zones of the left lung, moist rales bilaterally and prominent edema on the lower extremities. Chest X-ray showed a well-defined opacity filling the left middle and upper lung, and bilateral moderate pleural effusion. Computed tomography (CT) revealed a 12 × 9 cm mass in the left middle and upper lung and infiltrating the pleura. The complete blood count was unremarkable except for normochromic normocytic anemia (hemoglobin: 8 g/dL). Additional biochemical tests revealed hypoalbuminemia (1.8 g/dL), dyslipidemia and significant proteinuria (10 g/day) with granular and hyalin casts in urinary sediment. The erythrocyte sedimentation rate was 20 mm/h. Serum levels of C3 and C4 were found to be lower than normal limits: 45 mg/dL (normal: 55 – 120) and 10 mg/dL (normal: 14 – 51), respectively. Tests for antistreptolysin O titer, anti-nuclear antibody, cryoglobulins, hepatitis C antibody, hepatitis B surface antigen and HIV were negative. The pathological diagnosis of the tumor specimen obtained by CT-guided (fine-needle) aspiration was non-small-cell lung carcinoma (Fig. 1).

Radiotherapy was begun with 60 Gy towards the left hemithorax. Protein- and salt-sparing diet, furosemide (180 mg/day), amlodipine (10 mg/day) and ceftriaxone (2 g/day) were started. On the tenth day of hospitalization, deterioration of renal function (as evidenced by an increase in blood urea

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Departments of [1]Internal Medicine and [2]Pathology, Cukurova University Faculty of Medicine, Adana, Turkey 01330.

Address all correspondence to Saime Paydas, M.D., Cukurova University, Faculty of Medicine, Department of Internal Medicine, 01330 Adana, Turkey; e-mail: spaydas@cu.edu.tr

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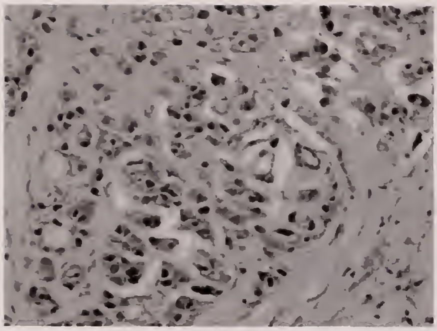

Fig. 1. Adenocarcinoma of the lung with gland forming.

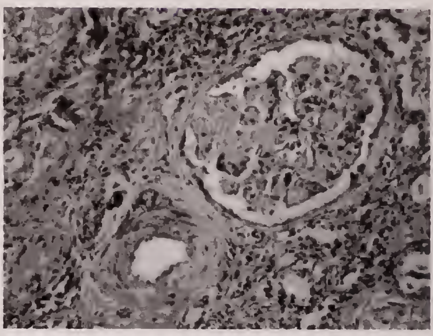

Fig. 2. Glomerulus with prominent mesangial and vascular deposition of amyloidosis (HEX 400).

nitrogen and serum creatinine) was detected (BUN: 105 mg/dL, normal: 8–20 mg/dL; Cr: 2.8 mg/dL, normal: 0.7–1.1 mg/dL). Ultrasonography and Doppler ultrasonography did not show evidence of obstruction, hydronephrosis or renal vein thrombosis. Subsequent renal biopsy was consistent with MPGN. Methylprednisolone (1 mg/kg/day), dipyridamole (225 mg/day) and aspirin (100 mg/day) were added to therapy for renal failure and nephrotic syndrome. However, the patient died on the 20th hospital day due to pulmonary failure from sudden massive pleural effusion.

Case 2

A 50-year-old man was referred to our hospital with nausea, vomiting, generalized edema, renal failure and proteinura. Renal function tests had been within normal limits one year earlier (BUN: 23, Cr: 1.2). Non-small-cell lung carcinoma (stage IIIB adenocarcinoma) had been diagnosed by fine-needle aspiration (FNA) on the left upper lung two years earlier. He had been treated with combination of radiotherapy (60 Gy to left hemithorax and mediastinum) and chemotherapy (every 4 weeks for 6 courses, using gemcitabine and cisplatin). Physical examination findings were generalized edema and no breathing sound on the upper zone of the left lung. Chest X-ray and CT of the lung showed a 10 × 10 cm mass in the left upper lung and mediastinal lymphadenopathy. Abnormal laboratory findings were as follows: serum level of albumin 1.6 g/dL, creatinine clearance of 8 mL/min, and proteinuria of 6 g/day. Renal biopsy showed amyloid deposition, secondary (AA) type (Figs. 2 and 3). Medical history was unremarkable for chronic infectious diseases like osteomyelitis, rheumatoid arthritis, familial hypotension or neuropathy and familial Mediterranean fever. Examination of amyloid deposition in lung tissue taken by FNA could not be done due to technical reasons. Renal function of the patient deteriorated progressively and required hemodialysis. Surgical resection of lung tumor was recommended for relief of paraneoplastic syndrome; however, the patient refused surgical intervention.

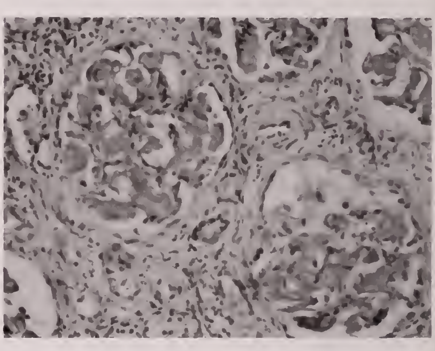

Fig. 3. Amyloid deposition with Congo-red stain (Congo-red × 400).

Discussion

Paraneoplastic nephrotic syndrome is seen concurrently with cancer diagnosis in 40% of cases and after the diagnosis of cancer in 20% of patients (3). In both of our cases, nephrotic syndrome was detected after the diagnosis of non-small-cell lung cancer. Membranous nephropathy is the most commonly seen glomerular lesion among cases of paraneoplastic nephrotic syndrome. However, the patient in case 1 had MPGN and the patient in case 2 had amyloidosis. Both these entities are reported uncommonly, especially amyloidosis, which is seen very rarely; only a few cases have been been reported so far (4).

The pathogenesis of paraneoplastic nephrotic syndrome has been thought to involve the production of cancer-related antigens, with subsequent damage to the glomerular basement membrane by antigen-antibody complexes. An alternative hypothesis is that an auto-antibody produced in response to the malignancy may cross-react and damage the glomerular basement membrane (3). MPGN, which is usually found in conditions of chronic infection or systemic disease, has rarely been seen in the course of carcinoma (5). It is assumed that the glomerular injury in patients with cancer and MPGN is mediated by circulating immune complexes, composed at least in part of tumor-associated antigens that may cryoprecipitate (6). Generally, the nephrotic syndrome completely resolves when the malignant disease can be treated curatively with chemotherapy and/or radiotherapy or surgery (7–9). Some immunosuppressive drugs (corticosteroids, cyclosporin and azathiopurine) have been found to be useful in a few cases (10). Our patient with membranoproliferative glomerulonephritis (case 1) died soon after treatment due to hypoxic-hypercapnic respiratory failure. For this reason there was insufficient time to observe the effect of immunosuppressive therapy.

Secondary amyloid (AA) deposition, found at renal biopsy in our second case, is unusual. In the literature, tumor-associated amyloidosis is frequently seen to be the AA type in renal cell carcinoma (4). Amyloid in association with tumors is usually primary amyloid (AL), and this has been described with bronchial tumors. However, there is one case report of carcinoma of the bronchus and renal AA amyloidosis (11) and there are some reports of amyloid deposits in basal cell carcinoma with permanganate resistance but without AA protein (12). It is speculated that intratumoral amyloid deposition could have a neoplastic origin rather than be a secondary amyloidosis. Amyloid may originate from the tumor cells as a result of tumor apoptosis (13, 14). In our case, the tumor could not be resected due to the patient's rejection of surgery, so we had no chance to determine the effect of tumor removal on the amyloidosis. Finally, nephrotic syndrome and renal failure did not improve. In this patient, amyloidosis could not be related to lung cancer. But we did not discover any etiology for renal amyloid deposition in his detailed medical history and laboratory evaluation. The second patient was also treated with nephrotoxic drugs such as cisplatin for 4 months. If he had had renal failure due to amyloidosis before lung cancer, the renal failure could have appeared earlier. But we cannot exclude other possibilities related to renal amyloidosis. In the literature, basal cell carcinoma and related amyloidosis seldom appear together (15). Earlier, we reported a case with basal cell carcinoma, tumoral amyloid deposition, renal failure and severe proteinuria. In that patient, renal failure and proteinuria regressed with tumoral resection and colchicine therapy (16).

In summary, we report two cases of non-small-cell lung cancer with nephrotic syndrome due to membranoproliferative glomerulonephritis and deposition of AA amyloidosis. These are rare occurrences, and the presence of renal pathology in cases with lung cancer produces a poor outcome.

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Unusual Polypoid Laryngeal Myxoma

Muhammad T. Idrees, M.D.[1], Richard Hessler, M.D.[2], David Terris, M.D.[3],
Charles Mixson, M.D.[3], and Beverly Y. Wang, M.D.[2]

Abstract

Laryngeal polyps, known as vocal cord polyps, are often benign, reactive, polypoid, squamous mucosa with subepithelial hyalinization and edematous stroma. Rarely, a benign mesenchymal myxoma occurring in the vocal cord will present as a polyp. It may have a local recurrence due to inadequate excision and result in airway obstruction. We report a case of a 46-year-old male who had a history of smoking and complained of hoarseness. A polypoid vocal cord mass was removed and the pathologic finding was a benign myxoma. To assure complete excision of the lesion, one should be aware that this rare entity may involve a laryngeal location.

Key Words: Laryngeal myxoma, polypoid mass, CD34.

Case History

A 46-year-old African-American male presented with complaints of hoarseness to an ear, nose and throat clinic in Georgia. His medical history was remarkable for hepatitis C, but he was otherwise healthy. The patient had a smoking history that was not quantified. Flexible laryngoscopy in the office revealed a polypoid lesion of the right true vocal cord. Suspension microlaryngoscopy was performed. It was noted that the lesion started on the right true vocal cord and extended to the anterior commissure. The lesion was excised with microlaryngeal scissors, providing a widely patent airway. Esophagoscopy, performed at the time of surgery, showed no other mucosal lesions. Pathological diagnosis was rendered and the slides were sent to the Mount Sinai Medical Center for consultation.

Microscopically, the lesion was polypoid and covered by laryngeal squamous mucosa with hyperkeratosis and parakeratosis (Figs. 1 and 2). There was no evidence of dysplasia. The submucosa was occupied by an ill-defined myxomatous neoplasm with no capsule (Fig. 3). The tumor bulged under the overlying mucosa, giving it the appearance of a

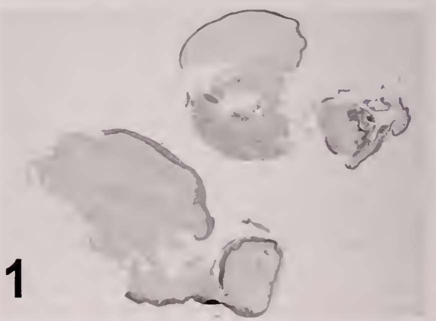

Fig. 1. Whole mount photograph showing a polypoid mass from vocal cord (×5, Hematoxylin-Eosin stain).

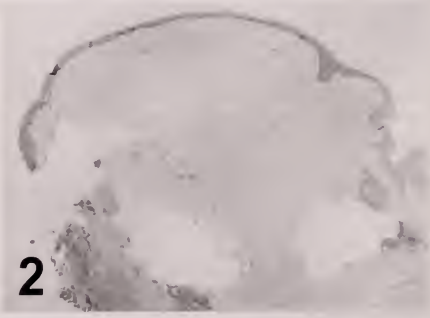

Fig. 2. Low magnification photomicrograph of laryngeal lesion, bulging the overlying squamous mucosa. No dysplasia is present in the surface squamous epithelium. Submucosa is occupied by a myxomatous lesion (×20, H-E stain).

From [1]The Lillian and Henry M. Stratton-Hans Popper Department of Pathology, The Mount Sinai Medical Center, New York, NY; and the Departments of [2]Pathology and [3]Otolaryngology, Medical College of Georgia, Augusta, GA.

Address all correspondence to Beverly Y. Wang, M.D., Department of Pathology, Medical College of Georgia, Augusta, GA 30912; e-mail: bwang@mcg.edu

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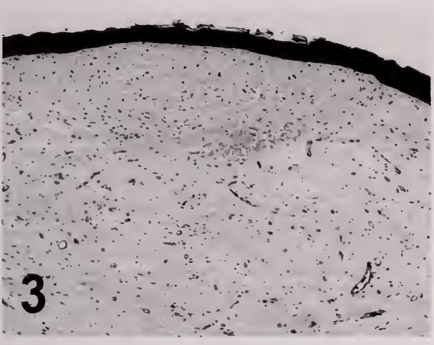

Fig. 3. Higher magnification showing myxomatous lesion with sparse spindled cells in a background of myxoid matrix (×50, H-E stain).

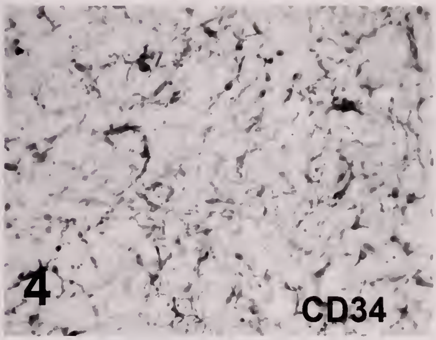

Fig. 4. Strong immunoreactivity of CD34 in tumor cells (×200, Streptavidin-biotin kit, immunohistochemistry).

polyp, with extension to the base of the excisional margin. The length of the tumor was 8 mm. Histologically, the lesion was paucicellular and composed of spindled cells dispersed in a background of abundant basophilic myxomatous stroma. The cellular population seemed monotonous, with spindly nuclei and abundant eosinophilic cytoplasm without vacuolization. No cellular atypia, pleomorphism or mitotic figures were observed. A few delicate capillaries were identified inside the tumor, without tortuousity or telangiectasia. Few inflammatory cells, mostly lymphocytes, were identified in the stroma. No red blood cell extravasation, hemorrhage or necrosis was seen. The overall impression was that of a benign myxoid mesenchymal spindle-cell neoplasm. Immunohistochemistry for S100 protein and CD34 were performed using a Streptavidin-biotin kit (BioGenex, San Ramon, CA); both tests were strongly positive (Fig. 4). Radiographic imaging was recommended, to exclude the possibility of a low-grade malignant lipomatous or chondroid neoplasm. The final diagnosis was a benign myxoma of the larynx.

Comments

Myxomas are benign mesenchymal tumors that occur mostly in subcutaneous soft tissue, intramuscular tissue or cardiac chambers. When they occur in the head and neck region, they mainly involve maxilla and mandible, subcutaneous tissue, and parotid gland (1). Rarely, they occur in the nasal cavity and the larynx. There are only sporadic cases of laryngeal myxomas reported in the literature in English (2–7). Within the larynx, the vocal folds (5, 6), aryepiglottic fold (3) and epiglottis (2) have been described as locations.

Myxomas are considered benign lesions and classified under tumor and tumor-like conditions of undetermined histiogenesis (8). Undoubtedly these are mesenchymal tumors, but unlike jaw myxomas, they are not of odontogenic origin. These soft tissue myxomas are thought to represent myxoid degeneration in tumors of mesenchymal origin (9). By gross examination, these lesions are usually polypoid in shape, and on cut section they show a glistening white matrix with gelatinous appearance. The tumor consistency ranges from very soft to moderately firm, depending on the cellular elements. The histologic appearance includes loosely dispersed stellate to spindle-shaped cells, with long, interlaced cytoplasmic processes lying in an abundant, poorly vascularized, mucopolysaccharide rich stroma and a variable meshwork of reticulin and collagen.

The most common clinical presentation is hoarseness and difficulty in breathing, which may be caused by airway obstruction requiring emergency tracheotomy (4). Supraglottic myxomas may become large and remain asymptomatic for a long time (9). Supraglottic myxomas as large as 6.5 cm have been reported (3, 10). Major differential diagnoses include myxoid degeneration of laryngeal polyp, which happens quite frequently and should be carefully excluded before rendering the diagnosis. Low-grade myxoid liposarcoma and chondrosarcomas can sometimes be very bland looking, and thus may mimic a myxoma. Correlation with radiographic studies is helpful. A more useful immunohistochemical stain is S100 protein, which is consistently negative for myxoma, but positive for lipoblasts and chondroblasts. Immunoreactivity of smooth muscle actin and CD34 can be seen in more than half of myxomas (11; Fig. 4).

Laryngeal myxomas can usually be excised endoscopically, but an external approach may sometimes be required. In previous case reports, they have been described in vocal cords. Benign myxoma has a propensity for local recurrence, due to its tendency to infiltrate surrounding tissues. Intraoperative frozen section is very useful for immediate assessment of margin status. Other case reports have described microscopic margin involvement without recurrence after many years. Therefore, surgical treatment with an adequate margin appears to be curative, with no further treatment other than follow-up (3).

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Introduction:

Innovations in Education at Mount Sinai

Mary R. Rifkin, Ph.D.[1],
Barry Stimmel, M.D.[2] and
Lawrence G. Smith, M.D.[3]*

The establishment of the Institute for Medical Education at the Mount Sinai School of Medicine in 2001 led to a renewed emphasis on the important role education plays in the training of the next generation of physicians and the need to reward faculty whose careers focus on education. The mission of the Institute is to assist educators to develop careers of distinction and professional satisfaction. To further this mission, the Institute launched several new initiatives that recognized scholarship in medical education, rewarded curricular innovation, highlighted education at Mount Sinai and its affiliated hospitals, and embraced mentorship and professional development among the faculty.

To highlight the efforts of faculty in curricular innovation, the Institute sponsored the first Educational Research Day in October 2003. Fifty faculty members submitted a total of 55 projects. The papers in this special issue of the *Journal* were chosen from posters presented on that Educational Research Day. These papers exemplify the diversity of educational activities at the Mount Sinai School of Medicine and its affiliated hospitals. They describe and analyze well-established educational programs, as well as new initiatives designed to improve the education of house staff and students.

The paper by Dr. Barry Stimmel describes the goals and objectives of the Mount Sinai Consortium for Graduate Medical Education, formed in 1996 and currently comprising 13 institutions and over 2,000 house staff. The Consortium's mission is to enhance and monitor the quality of house staff education across all specialties at participating hospitals. Dr. Stimmel describes the Consortium's educational programs and assessment activities and discusses some of its major accomplishments.

Drs. Rand David and Lawrence Reich created and evaluated a systems-based practice curriculum within the Primary Care Internal Medicine Residency program at Elmhurst Hospital Center, an affiliate of Mount Sinai Medical Center. In their article, they demonstrate that this curriculum, based on monthly small-group discussions focusing on systems-based practice, leads to an enhanced understanding of important topics in managed care. A greater awareness of the physician's role within the health care system enables the physician to offer optimal care to individual patients in a complex delivery system.

Another paper by Drs. Reich and David describes a competency-based assessment tool they developed for the Internal Medicine Residency program. This novel process focuses on outcomes of learning elements associated with the six core competencies of graduate medical education rather than on content and pedagogy. It allows for the assessment of both content and process-based features of each programmatic learning element together with its intended outcomes.

The paper by Drs. Lisa Bensinger, Yasmin Meah and Lawrence Smith reviews the importance of teaching skills curricula for residents, often referred to as Resident as Teacher (RAT) programs, their emergence over time, and their current status in graduate medical education. They also describe the Resident Teaching Development Program (RTDP), an expanding curriculum for all residents at the Mount Sinai School of Medicine and its affiliates. This seven-hour, multidisciplinary course was one of the first faculty development programs created by the Institute for Medical Education, in recognition of the critical role of residents as medical educators in our institution.

Marina Burke and Dr. Lawrence Smith describe a didactic and clinical curriculum, designed and implemented by four nurse practitioners in the Visiting Doctors Program at Mount Sinai, to provide home care exposure to third-year medical students. This program stresses a blend of medical, psychosocial and palliative aspects of patient care. Evaluation results indicated a high degree of acceptance on the part of the students of all aspects of the program, and suggest that nurse practitioners may be effective patient-centered-care role models for medical students.

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[1] Program Director, Institute for Medical Education, [2]Dean for Graduate Medical Education, and [3]former Dean for Medical Education, Mount Sinai School of Medicine, New York, NY

*Current position: Chief Academic Officer, North Shore Long Island Jewish Health System, Great Neck, NY.

The paper by Benjamin Kornitzer and Drs. Edward Ronan and Mary Rifkin presents the results of a study to determine whether the Summer Enrichment Program, a pre-matriculation program for selected students, eased their transition to medical school and enhanced their academic performance. The results show that this program, which previews four first-year medical school courses in a non-threatening, grade-free environment, has a positive impact on the enrolled students and plays an important role in improving the academic success of students who may not be optimally prepared for the rigors of medical school.

Suzanne Feigelson and Dr. David Muller created an elective, "Writing about Medicine," for medical students, in an effort to emphasize the role of humanism in medicine. Using reading and writing as its primary tools, this elective was Mount Sinai's first effort to encourage students to remain connected to patient-centered health care. The paper reviews two similar programs at other medical schools (SUNY Stony Brook and Columbia University) and describes the Mount Sinai curriculum. Positive evaluations from students have allowed this elective to be offered to all classes in the medical school.

To illustrate the work of first-year students in the "Writing about Medicine" elective, we present samples of their thoughtful, provocative writing.

Taken together, the papers in this special issue reflect some of the curricular innovations that have been developed to improve both medical student and house staff education at Mount Sinai School of Medicine and its affiliates. As the Institute for Medical Education continues its mission to provide a home base for teachers and to support and enhance educational creativity and scholarship at Mount Sinai, we hope to issue periodic reports on our progress in the *Mount Sinai Journal of Medicine*.

The Institute for Medical Education

Mary R. Rifkin, Ph.D., and Lawrence G. Smith, M.D.*

The Institute for Medical Education (IME) at the Mount Sinai School of Medicine (MSSM) was founded in 2001 to provide a "home base" for teachers and to support and enhance educational creativity and scholarship at Mount Sinai. The IME, thus, resembles other "teaching academies" at several other academic medical centers (1). In the few years since its inception, the IME has become a center for teaching excellence; it has promoted educational scholarship among the teaching faculty; it has encouraged curricular and teaching innovation for undergraduate, graduate, and continuing medical education; it has sponsored events that highlight the value of education in the life of Mount Sinai; and it has mentored teaching faculty in order to foster their professional development and academic advancement.

Membership and Benefits

Membership in academies or societies of teaching faculty at other institutions often requires nomination and selection and is often time-limited (2, 3). The IME at Mount Sinai is a comprehensive membership organization for all faculty, full-time or voluntary, of the School of Medicine and its affiliated hospitals. An on-line membership form has been created to simplify the application for membership, for all interested faculty. IME members include those faculty throughout the community who have expertise and/or interest in teaching the next generation of practitioners, who wish to share their ideas about education both at Mount Sinai and at their respective discipline-oriented national meetings, who wish to improve their teaching skills, who see teaching as an important component of their professional activity, or who devote scholarly effort to education research. The Institute currently has over 100 members.

Membership in the Institute entitles one to participate in the many professional development activities organized by the IME, including workshops and retreats; become eligible for small grant support for educational innovations; and receive a second letter of support for promotion on the clinician-educator track.

The IME has an appointed director, who is assisted in implementing Institute programs by a program director and program coordinator. The IME is monitored and guided by a 15-member Internal Oversight Committee (IOC), comprised of faculty with acknowledged reputations for excellence in the area of teaching and learning. The IOC meets twice a year.

Professional Development

The IME has created opportunities for faculty development throughout the entire teaching community, for specific groups (e.g., residents, students), and through customized educational experiences.

Education Leadership Conference

The goal of the Education Leadership Conference, sponsored annually by the Institute, is to provide an annual faculty development off-campus retreat for all course directors, clerkship directors, deans and other educational leaders at the MSSM and its affiliate institutions. The conference provides a forum for them to address the most challenging aspects of their roles and exchange ideas with their colleagues. This day also provides faculty with an opportunity to reflect on their roles as educational leaders and their continued professional development. In addition, it encourages communication among those who play key instructional roles in the undergraduate program at the MSSM, links colleagues and resources, and introduces new topics and ideas. Every year the conference has a new theme, such as "Evaluation," "Content Reform," and "Educational Leadership."

Sponsorship for National Programs

To develop leadership abilities of faculty, whether in the realm of education or administration, the IME helps faculty apply for highly competitive faculty development programs, such as the training course in clinical teaching sponsored by the Stanford Faculty Development Center, the Harvard-Macy Fellowship for Medical Educators, or the Harvard-Macy Institute's Program for Leaders in Medical Education.

Building the teaching skills of basic science educators is an important mission of the Institute.

From the Department of Medical Education, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Mary R. Rifkin, Ph.D., Box 1623, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

*Current position: Chief Academic Officer, North Shore Long Island Jewish Health System, Great Neck, NY.

Key Words: Medical education, teaching, education.

The IME has sponsored the attendance of faculty at the International Association of Medical Science Educators annual conference. As a result, many faculty members are more aware of nationwide issues and initiatives in the area of the basic science education of medical students.

Workshops

The IME offered a two-session Grant Writing Workshop in 2003. The workshop was primarily intended for Institute members who planned to write grant proposals to obtain funding for educational projects and research. The goal for each participant was to produce a working outline, including a rationale, for expansion and eventual submission. Twenty Institute members attended this workshop.

In 2004 the IME sponsored a two-session workshop that served to inform medical educators about methods for using “standardized patients” (SP) in teaching and assessment, and encouraged faculty to develop specific SP cases for teaching and/or assessment purposes. In the first session participants were introduced to the SP case template and discussed formats for SP use. Participants formed small working groups to generate ideas of how this methodology could be most effectively used in their own courses/programs, and subsequently teamed up in pairs to begin creating patient cases. In the second session, participants submitted their SP cases for review and comments by assigned facilitators.

Medical Education Grand Rounds

Every two weeks throughout the academic year, a seminar series features current topics in medical education, discussed either by invited speakers from other institutions or by Mount Sinai faculty. These seminars, offered to the entire faculty, bring visibility to education scholarship, innovative curriculum reform, and new programs to the entire institution.

Teacher Appreciation Day

Teacher Appreciation Day is held annually to honor outstanding faculty from the School of Medicine and affiliate hospitals of the Medical Center. Teacher Appreciation Day recognizes faculty who have achieved excellence in teaching. A monetary award and framed citation are given out at a reception to which all nominees and nominators are invited.

Promotions on the Educator Track

A faculty member’s contributions to teaching often go unnoticed in consideration for promotion. Mount Sinai recently revised its appointments and promotions process, adopting a Clinician and/or Educator Track in order to promote faculty who spend a significant part of their professional activities in clinical practice and/or education. Thus, although all faculty are expected to be competent as teachers, excellence in educational activities is now a primary criterion for promotion at Mount Sinai. And documentation of teaching scholarship is essential for evidence of educational excellence. Thus, the Director of the Institute will advise individual faculty members on the preparation of a teaching portfolio and help to prepare a Chair’s statement for the Appointments and Promotions Committee. In this way, as in others, the IME helps Mount Sinai faculty members to advance their professional careers.

Teaching Skills

Resident Teaching Development Program (RTDP)

The RTDP, under the leadership of nationally trained junior faculty, strives to improve the teaching and leadership skills of all our residents at Mount Sinai Hospital and its affiliates. The objectives of the program are (a) to create a curriculum that provides residents with practical teaching and leadership skills and is adaptable to the needs of any specialty; and (b) to increase residents’ confidence in their teaching ability and improve their attitudes towards their roles as teachers.

The daylong course is taught to postgraduate year 2 residents and consists of three core modules: Setting Goals and Expectations, Teaching Theory and Techniques, and Giving Feedback. Each module is approximately 2 hours in length. The program directors collaborate with chief residents and program directors of multiple departments to tailor the curriculum to each specialty. They have created relevant clinical case examples and role-plays that highlight issues unique to each department.

Resources relevant to this program are listed on the web, so that residents can readily access more information. The RTDP also fulfills many of the Accreditation Council for Graduate Medical Education competencies required for all graduate medical education training programs.

Teach the Teacher

Residents are often the primary teachers of interns and medical students in academic medical centers but are rarely given any formal preparation for teaching. Moreover, few faculty have the training to implement and teach a resident teaching skills program. The Teach the Teacher program is proving to be an effective means of training faculty to establish a teaching skills program in their own departments so that the education of residents as teachers becomes self-sustaining within a department. Faculty interested in teaching the curriculum attend a two-day workshop. The curriculum, as well as additional resources for teaching faculty, is available on the web.

Fourth-Year Student Elective—Becoming a Medical Teacher

In 2004 an innovative course on the "nuts and bolts" of adult learning principles and practical teaching techniques was offered for the first time to fourth-year medical students. This three-week elective course provides students with some formal training to excel as effective clinical teachers. The students go through the entire Stanford Faculty Development Program in Clinical Teaching Skills and attend small group sessions on various teaching techniques. Especially helpful are the opportunities that the students have to be videotaped while teaching and to receive extensive feedback on those teaching sessions.

Education Leadership Institute

Currently only a small handful of programs offer intensive teacher training to medical students, and there is a lack of any national train-the-trainer program for medical students interested in correcting this deficiency. In order to address this problem, the American Medical Student Association (AMSA), in partnership with MSSM and the IME, developed the first *Training Tomorrow's Teachers Today (T4)* Program in 2004.

The program is an intense five-day experience intended to provide medical students who are interested in academic medicine, with practical teaching and leadership skills. By the end of the week each student is expected to have developed a project to be implemented at his or her medical school. Thus far, the projects have ranged from sessions designed to cultivate teaching skills among fellow medical students, instructing resident physicians in effective methods of evaluation and providing feedback, and novel ways to increase medical student participation in curricular affairs.

Curricular Innovation

Educational Research Day

Educational Research Day is an annual event on campus that highlights the exciting, creative work in educational research, analysis and innovation taking place every day at Mount Sinai and its affiliates.

The half-day event includes a plenary session with an invited speaker, and a poster session at which posters by teaching faculty and house-staff are presented. The IME not only provides consultation for submissions, but also underwrites the cost of preparing the posters. A selection committee reviews all abstracts, which are published in an abstract book, and "blue ribbons" are awarded to selected posters for their excellence in curricular innovation. In addition, four posters are selected for presentation at the annual "Associate of American Medical Colleges Innovations in Medical Education" exhibit.

Website

To efficiently disseminate information about the IME's activities and also to serve as a resource for educators, the Institute maintains a website (www.mssm.edu/medschool/institute/index.shtml) that is constantly updated with new information for faculty. The website has on-line forms for membership application, abstract submission for Education Research Day, and nominations for Teacher Appreciation Awards. A new feature of the website is the "Education Spotlight," in which a faculty member or a program is highlighted in a question-and-answer format. Faculty are informed of new additions/updates to the website by e-mail, using the faculty listserv or Institute member listserv.

Summary

The Institute for Medical Education has developed a superb foundation upon which to build an outstanding center for the training of current and future medical educators and to nurture faculty who choose a career as educational leaders. While the Institute has already developed an impressive array of programs for its members and the education faculty at large, a number of initiatives remain to be developed.

The activities and events described in this report constitute a vibrant program for faculty development, teacher training, and curricular innovation in medical education. We anticipate that in the coming years, the Institute, by its broad range of programs, will help the Mount Sinai School of Medicine become a nationally recognized center for the training of medical educators.

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The Mount Sinai School of Medicine Consortium for Graduate Medical Education:

A Collaboration to Enhance Quality

Barry Stimmel, M.D.

Abstract

Over the years, the Graduate Medical Education (GME) programs have become increasingly complex; unfortunately, this trend has been accompanied by a decrease in federal funding. In 1996, in an attempt to enhance the GME effort, Mount Sinai School of Medicine formed its Consortium for Graduate Medical Education. At present the Consortium consists of 13 institutions and more than 2,000 house staff. It is completely self-supporting and has served to ensure the quality of residency programs at all participating institutions, while providing enhanced services to house staff.

Key Words: Graduate medical education consortia, Mount Sinai School of Medicine.

Introduction

The idea of consortia for graduate medical education is far from novel (1). In a 1993 survey of 437 major teaching hospitals and medical schools, 36 different graduate medical education consortia were identified, some of which had been in existence since the mid-1950s (2). Yet in that survey only one-fourth of the medical schools and a much smaller proportion of teaching hospitals were found to belong to consortia.

This lack of enthusiasm on the part of medical schools and academic medical centers was not matched by the policy-making organizations. As documented by Kelly et al. (2), the New York State Commission on Graduate Medical Education formally began to support consortia in 1986, and in the early 1990s, the consortium concept was endorsed by numerous educational and administrative bodies, including the Association of American Medical Colleges, the National Council on Graduate Medical Education, the Physician Payment Review Commission and, most important with respect to the Mount Sinai School of Medicine (MSSM), the New York State Council on Graduate Medical Education.

The strength of the council's interest was demonstrated when, subsequent to the passage of the Health Care Reform Act of 1996, it developed a two-year grant program to allow institutions within the state to form consortia at no cost to the participating institutions. With the desire to continually enhance the quality of graduate medical education, MSSM applied for and received a two-year grant to develop a graduate medical education consortium in 1996. The following is a description of the goals and objectives of the Consortium and an assessment of its ability to achieve these objectives over the past eight years.

Description of the Consortium

At present, the Mount Sinai Consortium for Graduate Medical Education consists of 13 institutions (Table 1), including hospitals in virtually every borough of New York City and 5 institutions in New Jersey (representing just under 10% of all teaching beds in that state). Within the Consortium are 176 programs training 2,260 house staff in virtually every specialty (Table 2). The Mount Sinai School of Medicine (MSSM) is the institutional sponsor for 10 of the participating institutions. The remaining 3 are their own institutional sponsors, with Mount Sinai serving as their major university affiliate.

Address all correspondence to Barry Stimmel, M.D., Dean for Graduate Medical Education, Box 1076, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

TABLE 1
Mount Sinai Consortium for Graduate Medical Education: Member Institutions

New York City
Bronx Veterans Affairs Medical Center*
Cabrini Medical Center*
Elmhurst Hospital Center*
Jamaica Hospital—Family Practice Residency Training Program*
Maimonides Medical Center
The Mount Sinai Hospital*
North General Hospital*
Queens Hospital Center*

New Jersey
Englewood Hospital and Medical Center*
Jersey City Medical Center*
Newark Beth Israel Medical Center
Saint Barnabas Medical Center
St. Joseph's Regional Medical Center*

*Sponsored by the Mount Sinai School of Medicine

TABLE 2
*Mount Sinai Consortium for Graduate Medical Education: Active Programs**

	Programs	Residents
ACGME-Approved	128	2,095
Non-ACGME-Approved	39	91
Board-Approved**	9	74
Total	176	2,260

ACGME = Accreditation Council for Graduate Medical Education.
*For 2003–2004 academic year.
**Refers to the American Board of Medical Specialties or the American Board of Podiatry or the American Board of Dental Medicine.

TABLE 3
Structure of the GME Consortium

Central GME Committee
Subcommittees:
Internal Review Committee
Committee on ACGME Core Competencies
Committee on Recruitment
Committee on Residency Size

ACGME = Accreditation Council for Graduate Medical Education; GME = Graduate Medical Education.

The Consortium is governed by a central Graduate Medical Education Committee (GMEC) chaired by the Dean for Graduate Medical Education, who is also the designated institutional official for the sponsoring institution. The members of the Consortium have agreed to abide by the rules of governance; to adhere to both academic and educational standards of the Consortium; to pursue its mission, goals, and objectives; and to provide ongoing financial support for Consortium activities. The central GMEC meets monthly, whereas its ad hoc subcommittees meet as needed, depending on the issues that arise (Table 3).

At the outset it was recognized that many of the policies and procedures of the members' residency programs would be within the bounds of those hospitals, since many of these policies transcend resident education. However, it was agreed that each sponsored program must meet the departmental standards set by the appropriate chairperson at MSSM, as well as the institutional standards set by the School. In addition, all member hospitals, regardless of whether they were sponsored by or affiliated with MSSM, agreed to comply with all Accreditation Council for Graduate Medical Education (ACGME) general requirements. Compliance was to be reviewed on a periodic basis by the central GMEC.

Each of the eight objectives of the Consortium (Table 4) is described in more detail below.

Objective 1: To Enhance General Educational Curriculum for All Specialties and Institutions

Core Curriculum for Entering House Staff

Two days prior to the start of each academic year, entering house staff from all institutions within the Consortium are brought to MSSM for a two-day seminar focusing on issues that are insufficiently addressed in medical school (Table 5). During the 2004–2005 academic year, more than 400 residents attended these sessions. Included in the curriculum were sessions required for certification by the Occupational Safety and Health Administration (OSHA) and the State of New York.

TABLE 4
Objectives of GME Consortium

1. To enhance general education of house staff
2. To assess residents and residency programs
3. To improve teaching resources
4. To establish uniform administrative policies
5. To develop an integrated computer network among institutions
6. To maximize participation in the GME Consortium
7. To meet the needs of communities served by Consortium members
8. To ensure financial stability

GME = Graduate Medical Education.

TABLE 5
Core Curriculum for Entering House Staff

Clinical decision making
Cross-cultural approaches to health care
Effective communication in emergency medicine
Use of mood-altering drugs/managing the impaired physician
Physician impairment: recognizing depression
House staff as teachers: resident-student interactions—Part I
HIPAA: what you need to know
Sleep deprivation: how to avoid it
The medical record and restraints: what not to do
Harassment
House staff as teachers: resident-student interactions—Part II
Medical informatics
The autopsy: advise and consent
GME Toolkit: resident/faculty evaluation software
Acute care of the hospitalized elderly
Emergency preparedness
Recognition of child abuse and domestic violence
Principles of palliative care
Credentialing
Levy Library resources and services
Recreational opportunities
Infection control
Fitting respiratory masks

HIPAA = Health Insurance Portability and Accountability Act of 1996; GME = Graduate Medical Education.

TABLE 6
Chief Residents Retreat Agenda

Medical errors
Role of the chief resident as a teacher
Role of the chief resident as a manager
Systems-based practice and practice-based learning: what is a chief resident to do?
Common adjustment problems seen in residency
Physician impairment
Summary of facts and circumstances
Regarding two patients
Risk management guidelines for medical residents
Record documentation
Moot court
Disparities in health care
The Bell Commission, the physician workforce, and the ACGME duty hours standards

ACGME = Accreditation Council for Graduate Medical Education.

Chief Residents Retreat

Each year, incoming chief residents in all the core specialties leave the city for a two-day retreat addressing administrative issues and educational leadership (Table 6). During the 2004–2005 academic year, a total of 90 chief residents from all the member institutions participated.

Consultant Teams

Faculty at the School of Medicine are available to travel to residency programs at member institutions, to provide intensive seminars on Residents as Teachers, Cultural Diversity, and Ethical Issues in Medicine.

Objective 2: To Assess Residents and Residency Programs

Clinical Assessment of Entering House Staff

In June, July and August or in January and February, residents beginning their training participate in a clinical assessment involving standardized patients at the school's Morchand Center. Each resident is provided with an analysis of his/her performance, and distribution curves illustrating how his/her performance compares with that of the cohort of residents taking the examination and with that of the senior student cohort that takes this examination in the year prior to graduation. The residents also receive a videotape of their performance, which they review with the program director, to learn how their interpersonal, history taking, and physical examination skills can be enhanced. Program directors receive a demographic analysis that summarizes resident performance by specialty, country of graduation, institution, and prior experience with standardized patients.

Clinical Assessment for Remediation

Residents who are advanced in their training but whose skills in history, physical examination, or interpersonal communication are found to be deficient are given an opportunity to have their skills reassessed at the Morchand Center. Appropriate information is provided to program directors so that remediation can be obtained.

Internal Reviews

Each sponsored residency program within the Consortium is reviewed at the midpoint between scheduled Residency Review Committee (RRC) visits to ensure compliance with both ACGME and Consortium standards. The results of internal reviews—as well as formal RRC reviews and ACGME status for each residency program—are reviewed and discussed at the monthly meetings of the central GMEC. When weaknesses are identified within a program, the internal review committee may suggest that another Consortium member provide the resources to rectify the deficiency or that quality can best be maintained by integrating or merging the specific programs.

Objective 3: To Improve Teaching Resources

The Institute for Medical Education at the MSSM provides in-house faculty development seminars and sends out visiting teams of faculty to participating institutions. In order to provide self-enhancement incentives to faculty, a Teacher Appreciation Day is held each year to select faculty members for awards based on their teaching skills.

Objective 4: To Establish Uniform Administrative Policies

The Consortium recognizes the importance of permitting each institution to fine-tune uniform policies for residents in such areas as benefits, evaluation and advancement, and due process. A house staff policy manual is revised and updated biannually and placed on the GME website. This allows participating institutions to access the material, making appropriate modifications to meet their requirements while maintaining the ACGME standards and Consortium goals and objectives. A manual for program directors is also provided to address the issues of program administration and compliance with institutional and State requirements.

Objective 5: To Develop an Integrated Academic Network

GME Toolkit is a platform used by member institutions to meet the requirements for reporting house staff demographic information to the GME Consortium office. It allows entry of demographic information on house staff, scheduling of resident rotations with automatic distribution of evaluations to supervising faculty, and monitoring of resident duty hours. It is also possible to use the system for resident credentialing and privileges.

Objective 6: To Maximize Participation in GME Consortium Activities

In addition to the monthly meeting of the GMEC, institutions having more than one residency program participate in Dean's committees, in which the Dean and selected chairpersons of MSSM and representatives of the institution meet to review clinical and educational issues. Resident participation in Consortium activities is maximized by having residents participate in the GME Committee and subcommittee meetings and in internal review committees.

The activities of the GME Consortium with respect to resident supervision, responsibilities, evaluations, and compliance (with both Consortium and ACGME standards) are communicated to the medical staff of participating institutions in the form of an annual report. At this time clinical interactions between each participating institution and other members of the Consortium are discussed.

Objective 7: To Meet the Needs of Communities Served by Consortium Members

Our institutions are located in communities that are exceptionally diverse. To enhance the Consortium's ability to attract residents reflective of these institutions' communities, the school sponsors a Senior Electives Program. This program allows underrepresented minority medical students from across the country to take electives at Consortium institutions during their senior year, prior to submitting their matching list to the National Resident Matching Program.

In order to encourage physicians to remain within the area served by member institutions, career-planning seminars and a job website for residents completing their training are provided. The career-planning seminar agenda includes ways to select a private practice setting, how to pay off debts incurred while in medical school and residency training, and what to look for when reviewing contracts for private practice opportunities. The website, which is available to residents who are in their last year of training, lists more than 300 positions in all specialties.

Objective 8: To Ensure Financial Stability

Finally, to achieve our goals and objectives it is essential to have adequate, stable financing. Unlike some other consortia, there is no "pooling" of financial resources to provide financial support (3). As noted earlier, the Consortium was first established with the assistance of a two-year grant from the New York State Education Department. At that time, the chief executive officers of all participating institutions agreed that if the Consortium were considered a worthwhile endeavor, each hospital would continue to contribute to its support. Their initial evaluations were sufficiently favorable to ensure continuous support. While at that time only eight hospitals were members of the Consortium, five other institutions became members after reviewing Consortium activities, bringing the total enrollment to its current size. Hospitals contribute funding based on the number of ACGME-approved programs within each institution. This has allowed for stability and permitted the Consortium not only to continue but also to expand its programs when deemed appropriate by the GMEC.

Conclusion

In summary, the Mount Sinai School of Medicine's GME Consortium continues to meet its objectives and is a valuable resource to all participating members. In an era when most medical institutions are experiencing some degree of financial distress, it is gratifying to note that the value of the Consortium continues to be recognized by all of its members in their support of its activities.

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The Creation and Evaluation of a Systems-Based Practice/Managed Care Curriculum in a Primary Care Internal Medicine Residency Program

RAND A. DAVID, M.D., AND LAWRENCE M. REICH, M.D.

Abstract

Background: A systems-based practice (SBP) is defined by the Accreditation Council for Graduate Medical Education as "manifested by actions that demonstrate an awareness of and responsiveness to the larger context and system of health care and the ability to effectively call on system resources to provide care that is of optimal value" (1). We developed a systems-based practice / managed care curriculum in a monthly workshop format, and integrated it into our Mount Sinai School of Medicine (Elmhurst) program in internal medicine. We evaluated the success of this workshop by utilizing both subjective and objective assessments of knowledge obtained by medical residents in attendance.

Methods: We surveyed our medical residents in order to assess their educational experiences in the workshop with regard to their comfort level with the use, application, and discussion with patients of 13 concepts central to current SBP issues, as well as to what extent they believed the workshop improved or enhanced this level of comfort (subjective assessment). Residents then completed10 *true/false* questions designed to measure their understanding of key SBP points (objective assessment). Their performance on this section was evaluated based on their individual experiences with the workshop.

Results: The mean comfort level for all 13 SBP topics increased via Likert scale from 2.79 before participation in the workshop, to 3.51 after participation. The mean comfort level improved for 11 out of the 13 topics (only "Medicaid" and "Medicare" did not show this improvement). Results of the 10-question test revealed that the mean percent correct score was lowest for those who did not attend the workshop (60% for interns and 67% for residents), intermediate for those who attended once (78%), and highest for those who attended more than once (84%). Of those who attended at least once, senior residents scored slightly lower than interns and junior residents (78% vs. 81%); the difference was not statistically significant.

Conclusion: The inclusion of an SBP curriculum can increase internal medicine residents' understanding of, and comfort with, important topics in managed care and SBP.

Key Words: Systems-based practice, managed care, core competency.

Background

A FAMILIARITY WITH SYSTEMS-BASED PRACTICE (SBP) is one of the six required core competencies of graduate medical education (1). As described by the Accreditation Council for Graduate Medical Education (ACGME), "residents are expected to demonstrate an awareness of and responsiveness to the larger context and system of health care, and the ability to effectively call on system resources to provide care that is of optimal value" (1). We have developed relevant sections in our ambulatory care curriculum in order to address this goal. These sections include community medicine, social aspects of medicine, legal medicine, occupational and environmental medicine, laboratory medicine, evidence-based medicine, as well as our curriculum in managed care. Additionally, we have borrowed material (with permission from the Tufts Health Care Institute's *Curriculum Guide on Managing Care: A Systems-Based Approach* and the Federated Council of Internal Medicine (FCIM) curriculum) to create a focused SBP curriculum most applicable and appropriate to our own practice and learning settings (2, 3). The goal of this SBP curriculum is to train residents to:

- understand, access and utilize the resources, providers and systems necessary to provide optimal care;

From the Department of Ambulatory Care, Mount Sinai Services, Elmhurst Hospital Center, Elmhurst, NY.

Address all correspondence to Rand A. David, M.D., Director, Department of Ambulatory Care, Elmhurst Hospital Center, 79-01 Broadway, Suites D1 – 24, Elmhurst, NY 11373.

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- understand the limitations and opportunities inherent in various practice types and delivery systems, as well as those processes especially prone to error, and develop strategies to optimize care for individual patients;
- apply evidence-based, cost-conscious strategies for the prevention, diagnosis and management of disease; and collaborate with other members of the health care team to assist patients in dealing effectively with complex health care systems and to improve processes of care;
- understand the role of the system in facilitating medical errors, and suggest ways of improving the system as these problems are discovered; and
- apply their sense of professionalism and practice-based learning towards their ability to understand their own role in committing and/or admitting errors, and focus on improvement of themselves as well as the system within which they work.

Within the Mount Sinai School of Medicine (Elmhurst) Program in Internal Medicine, we created, implemented, and evaluated an SBP curriculum with the above goals in mind. The curriculum is distributed prior to a small group workshop, via self-learning slide presentations and other (written) syllabus materials on electronic files. This material is kept at a workstation available to all medical residents as well as on our program's intranet website. Then, in small group settings of 8–12 medical residents and a faculty facilitator, a senior medical resident leads a 90-minute discussion on the curriculum. These SBP workshops occur on a monthly basis, and over three years of medical residency each resident attends three such workshops, one of which he/she leads. Additionally, the senior resident completes a 25-question test prior to the workshop. After the workshop the facilitator evaluates the senior resident's presentation and test performance, and the results of both are included in the resident's file. What follows is a summary of our evaluation of the curriculum's effectiveness.

Methods

All 36 residents in our program as of June 2001 were asked to complete a questionnaire designed to assess their educational experiences in the SBP workshop over the preceding year. This questionnaire asked them to rank, on a 5-point Likert scale, their comfort level with the use, application, and discussion with patients of 13 concepts central to current managed care (MC) issues, and to then assess to what extent the SBP workshop improved or enhanced this level of comfort. They were then asked 10 *true/false* type questions designed to assess their understanding of key MC points (Table 1). Their performance on this section was evaluated based on their individual experiences with the MC workshop.

TABLE 1

True/False Assessment Test

1. In a capitated program, patients need to pay more if they see their doctor more.
2. Most Medicaid recipients in New York State are enrolled in managed care plans.
3. The first HMOs (health maintenance organizations) in the United States date to the mid-1980s.
4. A staff model HMO is generally a closed-panel HMO.
5. An IPA (independent practice association) is generally associated with an open-panel HMO.
6. In general, members of Medicaid managed care plans are able to visit sub-specialists without first seeing their primary care provider.
7. In New York, nurse practitioners are able to write prescriptions for medication.
8. Currently, Medicaid does not provide coverage for any prescription medication.
9. Medicare provides coverage for long-term home health care.
10. There are no "fee-for-service" patients seen in our Medical Primary Care Clinic.

Results

Twenty-two of 36 (61%) of medical residents responded to the survey. Of these, 9 of 22 respondents (41%, including 6 interns and 3 junior and senior residents) had never attended the MC workshop, 8 (36%) had attended a single workshop, and 5 (23%) had attended the workshop more than once. The 13 (59%) medical residents who had attended the workshop at least once included 6 senior residents and 7 interns and junior residents. The mean comfort level for all 13 MC topics increased from 2.79 before participation in the workshop, to 3.51 after participation (see Tables 2 and 3). Looked at individually, the mean comfort level was seen to improve for 11 of the 13 topics. Only "Medicaid" and "Medicare" did not show this improvement, due to their generally higher baseline levels of comfort.

The performance on the 10-question test was clearly related to experience in the workshop (Table 4). The mean percent correct score was lowest for those who did not attend the workshop (60% for interns and 67% for residents), interme-

TABLE 2

*Residents' Level of Comfort with Managed Care Terms **Before** Participation in Workshop*

Term	All Residents	PGY-1	PGY-2	PGY-3
Capitation	2.6	2.5	2.2	3.0
Fee-for-service	3.5	4.0	3.2	3.6
Co-payment	3.5	3.5	3.0	4.0
Deductible	2.8	2.5	2.0	3.7
Gatekeeper	2.4	3.0	2.2	2.4
HEDIS	1.6	1.5	1.6	1.6
Out-of-pocket cost	3.1	1.5	2.8	3.8
Pre-certification	2.7	1.5	2.6	3.2
HMO	3.3	3.5	3.0	3.4
PPO	2.4	3.5	2.8	1.6
HCFA	1.4	1.5	1.6	1.2
Medicaid	3.5	4.0	3.0	3.8
Medicare	3.5	4.0	3.0	3.7

PGY-1 = postgraduate year one
HEDIS = Health Employer Data and Information Set
HMO = health maintenance organization
PPO = preferred provider organization
HCFA = Health Care Financing Administration

TABLE 3

*Residents' Level of Comfort with Managed Care Terms **After** Participation in Workshop*

Term	All Residents	PGY-1	PGY-2	PGY-3
Capitation	3.5	3.5	2.8	4.2
Fee-for-Service	3.9	4.0	3.6	4.2
Co-payment	3.8	3.5	3.6	4.2
Deductible	3.5	4.0	2.8	4.0
Gatekeeper	3.5	3.0	2.8	4.4
HEDIS	3.2	3.0	2.4	4.3
Out-of-pocket cost	3.4	3.2	2.8	4.0
Pre-certification	3.3	2.5	2.6	4.2
HMO	3.7	4.0	3.0	4.2
PPO	3.7	4.0	3.0	4.2
HCFA	3.1	2.5	2.4	4.3
Medicaid	3.5	4.0	3.0	3.8
Medicare	3.5	4.0	3.0	3.8

See Table 2 for definitions of all abbreviations.

diate for those who attended once (78%), and highest for those who attended more than once (84%). Of those who attended at least once, senior residents scored slightly lower than interns and junior residents (78% vs. 81%); the difference was not statistically significant.

TABLE 4

Resident Performance (Percent Correct) on 10-Question Test

Residents' Experience	n	Mean Percent Correct
Did not attend (PGY-1)	6	60
Did not attend (PGY-2, 3)	3	67
Attended once	8	78
Attended more than once	5	84
Attended (PGY-3)	6	78
Attended (PGY-1, 2)	7	81

PGY-1 = postgraduate year one

Conclusions

We have demonstrated that the creation and implementation for medical residents of an SBP curriculum via a workshop format can enhance both learning and comfort levels with a number of topics vital to this core competency. However, it is important to remember that, given the broad scope of the SBP competency, ranging from medical errors and performance improvement to Medicare and various payment systems, there is no clear consensus as to exactly what constitutes a complete SBP curriculum. One compelling argument would be to follow the Institute of Medicine and the Joint Commission on Accreditation of Health Care Organizations' lead in focusing on aspects related to patient safety (4, 5). Both encourage a focus on patient-centeredness, enhanced systems' communication, and delivery of care that is effective, efficient, and equitable for all patients. Quality and consistency are recurrent themes.

A greater awareness of one's role within the health care system generates a clear opportunity to contribute to the system's improvement. Physicians, who are frequently aware of barriers to their patients' treatments, as well as the processes especially prone to error, are perfectly positioned to offer and execute ideas that can lead to positive change. And physicians who are aware of these issues are better able to offer optimal care to individual patients in a complex delivery system. However, it has been very difficult to effectively teach these SBP topics to residents. Residents often note being "bored" with these topics, seeing them as a diversion from learning "real" medicine. This presents great challenges to educators in designing an adult learner centered curriculum. The idea of enlisting the residents themselves in the process, and providing them with the knowledge needed to lead a small group workshop presentation, appears to create a more engaging learning atmosphere for workshop attendees. The process effectively empowers one member of the peer group, allowing that individual to become the champion of a new topic in a way that elevates the interest level of everyone involved. This appears to us to be the key to our success. The specific content chosen for the curriculum is easily changeable. And there are certainly differences of opinion as to exactly what topics are most critical to optimum competency in SBP. But the approach of "training a trainer" resident appears to be one secret of our success that could be easily duplicated, despite differences in the specifics of the didactic material.

One of our senior residents became so fascinated by SBP that upon graduation she enrolled in a master's program in public health, the first to do so in our program's history. Several others have expressed greater confidence in their ability to better select a practice that is right for them. Perhaps if we teach them correctly, as senior residents, they will be better able to appreciate that knowing how to deliver medical care is as important as actually knowing what to deliver.

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Comprehensive Educational Performance Improvement (CEPI):

An Innovative, Competency-Based Assessment Tool

Lawrence M. Reich, M.D. and Rand A. David, M.D.

Abstract

Background: The focus of competency-based training is on outcomes, specifically well-trained residents. Our goal is to help move resident assessment away from content- and process-based factors and towards measures of mastery of practice. Doing so requires reorganizing and reprioritizing elements of the training program. We describe our attempt to shift the priorities of our program (the primary care internal medicine residency of the Mount Sinai School of Medicine [Elmhurst] Program) towards the desired outcomes of the medical resident, faculty, institution, and program as a whole. These outcomes are based on the six core competencies of graduate medical education (medical knowledge, patient care, interpersonal and communication skills, professionalism, systems-based practice, and practice-based learning and improvement). We call this process "comprehensive educational performance improvement" (CEPI).

Methods: We began by identifying each individual learning element of the program and classifying it into a clinical, didactic or evaluative "domain." We thus identified 40 clinical learning elements (specific outpatient and inpatient clinical settings), 25 didactic learning elements (specific lecture formats, workshops, conferences, etc.), and 11 evaluative elements (evaluation formats and contexts). Then we developed a set of questions intended to define and evaluate each element. Finally, we established criteria for prioritizing these questions, by asking relevant faculty, staff, and residents to assign priority scores for each.

Results: By this process, we generated 2 – 6 questions for each learning element, resulting in a total of 301 questions. This constituted a comprehensive plan for the assessment of both the program and the competency of the medical residents who have completed the program. Examples of the application of this process are described.

Conclusions: The CEPI process has a number of strengths. It allows for the concurrent assessment of each learning element with its intended outcomes, enabling us to simultaneously assess its outcome and its programmatic value. It effectively integrates the cognitive aspects of a program element with its clinical aspects, along with the input of evaluators at various levels. Finally, it helps train faculty members in an evidence-based approach to the curriculum.

Key Words: Medical education, medical residencies, assessment, evaluation, curriculum, accreditation, core competencies.

Background

For centuries, medical training was based on an apprentice system. Through extensive observation and imitation of an appropriate medical role model, the trainee would supposedly gain the knowledge and skills needed to become an independent practitioner. Although this system served medical education for centuries, it is no longer appropriate in the modern era. The reasons include the ever-expanding volume and complexity of medical knowledge, the development of modern technology, the growing complexity of medical and social systems, and society's changing perceptions of the roles, responsibilities and accountabilities of physicians (1).

Two paradoxes typify the difficulties inherent in training doctors in the modern era. The first paradox is that it is possible for a medical trainee to be in possession of an enormous amount of medical knowledge and still not be an effective physician. The second is that it is possible for a trainee to have all the skills necessary to be an ef-

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Assistant Professors of Medicine, Mount Sinai School of Medicine and Department of Ambulatory Care, Mount Sinai Services, Elmhurst Hospital Center, Elmhurst, NY.

Address all correspondence to Lawrence M. Reich, M.D., Department of Ambulatory Care, Elmhurst Hospital Center, 79-01 Broadway, Suites D1-24, Elmhurst, NY 11373.

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fective physician and still not be able to direct these skills towards effective patient care. It is partly in response to these two paradoxes that the Accreditation Council for Graduate Medical Education (ACGME) has promulgated a search for novel approaches to medical training. Towards this goal, it has addressed the first paradox by the organization of the "domains" of medical education (clinical, didactic and evaluative) into six core competencies (*medical knowledge, patient care, interpersonal and communication skills, professionalism, systems-based practice, and practice-based learning and improvement*), and addressed the second paradox by the promotion of its "outcome project," which emphasizes that the most appropriate assessment of the outcomes or results of medical training is the demonstration of actual clinical performance, not presumed potential clinical performance (2–4).

How do the ACGME's core competencies address the first paradox? Clearly, a trainee may have an abundance of *medical knowledge regarding patient care*, but lack an understanding of how to ensure that a given patient can actually receive that care by overcoming barriers to access (*systems-based practice)*, or else be unable to effectively communicate with the patient in a way that the patient understands (*interpersonal and communication skills*). And the trainee would not be able to assume an effective physician's role in society without mastering the competency of *professionalism*. Nor would he or she be able to carry out ongoing self-correction or the lifelong updating of clinical skills without mastering the competency of *practice-based learning and improvement*. But demonstrating or assessing that the trainee has mastered these competencies, while necessary, is not a sufficient goal of medical training. The focus must then shift to the outcome of a well-trained resident who has demonstrated the ability to function as an independent practitioner. Thus, we must assess and ensure the *actual* effectiveness of training as opposed to its *potential* effectiveness. Looking at the actual effectiveness of training requires a set of questions that differs in intent from those previously asked (3). Previously, it was sufficient to ask, "Do clear learning objectives of appropriate content exist, and is the resident appropriately exposed to settings in which they can be achieved?" The new focus now must ask, "Do the residents actually achieve the learning objectives in a meaningful way, and how can this achievement be demonstrated to contribute to the resident's performance as a practitioner?" A new set of priorities (clearly identifying learning objectives, assessing the attainment of these objectives, and using these data to facilitate the continuous improvement of both the residents' and the program's performance) is also required (3).

With our training goals in mind, we describe in this report the process by which we refocused the priorities of our program (the primary care internal medicine residency of the Mount Sinai School of Medicine [Elmhurst] Program) in light of the professional needs and desired outcomes of the medical residents, the faculty, the institution (Elmhurst Hospital Center), and the program as a whole.

Methods

While revising the written curriculum for the residency program, we examined the role that each component of the program played in the process of resident education and training. Previously, our curriculum (like other traditional curricula) had been organized around *content* (what we taught) and *process* (how we taught it).

Our goal, in accordance with ACGME guidelines, was to reorganize it around *outcomes* (3). Thus, the relevant questions are not "Is this what we want the resident to know?" (i.e., a content-based curriculum), or "Is this the best way to teach this material?" (i.e., a process-based curriculum), but rather, "Does the presence of this content and process in the curriculum help us to train a resident who can master the competencies of practice?" (i.e., an outcomes-based curriculum).

In the process of envisioning this reorganization, we developed an approach that we call "comprehensive educational performance improvement" (CEPI). As a first step, we endeavored to identify each individual, distinct learning element (LE) of the program and classify each LE into its clinical, didactic, or evaluative domain. LEs (defined as the "specific settings, contexts and methods in or by which resident education and training occur") were identified by a review of the formal written curriculum as well as from discussions with residents. Clinical LEs would include specific inpatient (e.g., general medical wards, critical care units) and outpatient (e.g., medical clinic, nephrology clinic, emergency room) settings in which the residents rotated. Didactic LEs would include lectures, conferences and workshops in which the residents participated. Evaluative elements included evaluation formats and contexts other than those specific to the clinical and didactic learning elements (see Table). Then, we applied to each LE a set of general questions intended to define and to describe, qualitatively and quantitatively, the programmatic value of each LE. These questions were the following:

- Can this LE be categorized into one or more of the core competencies?
- Can its actual effectiveness (its outcome) be described or measured in terms of the resident's performance?
- How does this LE specifically further the educational goals of the program?
- Is this the most effective modality for teaching and learning this specific content?
- Does this LE provide the proper balance between education and service?
- Does this LE have a measurable impact on the resident's professional development?
- Is its inclusion in the program consistent with the needs of the institution?

Applying these general questions, when appropriate, to each of the distinct programmatic LEs produced a compendium of more specific questions. And each of these specific questions, as will be described below, represents a potential educational performance improvement (PI) project. Recognizing the impossibility of undertaking all of these potential PI projects, the final step is to prioritize them, by asking relevant faculty, staff, and residents to go through the compendium of questions and to assign priority scores for each of them, as well as to suggest how to address each of them. This process can be used to assess the program and the competency of the residents, as well as suggest ways to improve both.

Results

By the process described above, we identified 40 distinct clinical LEs (specific outpatient and inpatient settings through which the residents rotated or performed service in the course of the program) and 25 didactic LEs (specific lecture formats, workshops, conferences, etc., in which the residents participated over the course of the program). Additionally, we included 11 evaluative elements (additional evaluation formats and contexts other than those specific to the clinical and didactic learning elements). We approached these evaluative elements (Table) with a similar set of criteria, asking if they were the best, most appropriate, or most useful methodologies, and if they furthered the programmatic goals of the residency, as well as if they were competency-based. Evaluative elements included those that were in current use, being reviewed for modification, or being proposed or under consideration. Our approach was to identify the components of the evaluation, identify how they were being implemented, and identify their desired goals and outcomes.

TABLE

Evaluative Programmatic Learning Elements

Nurse evaluation
Mini-CEX, clinical evaluation exercise
Rotation-based multiple choice question exam
Evaluation by ancillary hospital staff
Patient evaluation
Peer evaluation
Review of videotaped patient encounter
Evaluation of research project
Chart audit—outpatient progress note
Chart audit—hospital discharge summary
Monthly evaluation form

CEX = clinical evaluation exercise.

In the next step, by attaching each potential question to each LE, and then with the assistance of relevant personnel, identifying which questions made the most sense or were the most important to address, we came up with between two and six appropriate questions for each of these 76 learning elements, resulting in a set of 301 questions. Sample pages from this 76-page compendium, illustrating its general format and representative questions, are shown (Figs. 1–3). Individually, each of these questions represents a potential educational PI project, but the compendium as a whole represents both a blueprint of where the program is now, as well as a roadmap of where the program needs to go in order to achieve a relevant outcomes-based assessment.

The following cases will highlight the utility of this process.

Case 1: Didactic Small-Group Workshop

For the past several years, Dr. S. has been running a monthly small-group workshop as part of a series of ambulatory care teaching workshops. Her workshop focuses on a specialty outside of internal medicine, but integral to the training of the general internist. The format for this workshop has been a review of general topics in this specialty, with discussions of practical management issues in diagnosis and therapy. Dr. S. had some concerns about the value of her workshop in the overall training of the residents who attend it. She was concerned that the residents might have difficulty in applying the content to the clinical setting, that this was not the most effective or efficient format for teaching this material, and that the workshop was not contributing in a meaningful way to the residents' overall development. Recognizing that merely identifying this clinical content as important material to know was insufficient grounds for continued inclusion of

Fig. 1. *Sample CEPI page, clinical outpatient service.*

Component: MPC-Pap Smear Service
Category: Clinical
Setting: Outpatient clinics
Faculty: Dr. A.
Description Residents see MPC patients for cervical cancer screening
Competencies: All

Question	Assessment	Competency	Personnel	Priority
Do residents find this rotation to be clinically useful?	Resident survey	All	Chief resident	
Is there a proper balance between service and learning?				
At the conclusion of this rotation, does the resident feel competent to perform a Pap smear?				
Is this an effective modality for learning this content?	Assessment of resident's mastery of this content, assessed by Board performance, in-service exam, or patient outcomes.		Dr. A	
Does this rotation have an impact on the resident's professional development?	Reflective learning: "Can you recall a particular experience you had in this rotation that was important to you?"	Professionalism		

Comments:

the workshop in the program, we applied the CEPI approach to competency-based outcomes assessment. An instrument to objectively assess the acquisition of medical knowledge in this area (a multiple-choice question test) was developed, and external objective assessments (e.g., performance in this area on the in-service exam) were looked for. A questionnaire designed to assess the residents' subjective experience in this workshop was also developed—this questionnaire asked the residents to rank the importance to them of their experiences in the workshop, according to the criteria established by the competencies of *medical knowledge* and *patient care*. They were also asked to assess its value to them in terms of their professional development and in their actual ability to apply what they had learned in clinical settings. As a result of these assessments, Dr. S. was able to modify the curricular content and learning objectives of the workshop to be more congruent with the residents' needs. She was able to have a better sense of the stage of training in which the workshop would have the most impact on the residents' clinical care, and also a better sense of the value of the workshop in the residents' professional development. The process also left Dr. S. with a heightened sense of professional satisfaction, knowing that she was maximizing her effectiveness as an educator, as well as participating in outcomes-based education research.

Case 2: Outpatient Clinical Experience

For many years, residents have been rotating on an elective basis through an outpatient experience in Dr. P.'s clinic, in which they encountered tertiary referral patients suffering from an uncommon (outside of this clinic) disease. Since most residents would not, in the course of their professional careers, be responsible for the management

Fig. 2. *Sample CEPI page, didactic small group workshop.*

Component: Poetry Workshop
Category: Didactic
Setting: Small-group workshop
Faculty: Dr. R.
Description Monthly workshop in which poetry dealing with issues such as doctor-patient communication, the experience of illness, the experience of being a physician, and other relevant issues, is presented for discussion.
Competencies: Professionalism, interpersonal skills and communication, patient care.

Question	Assessment	Competency	Personnel	Priority
Do residents find the Poetry Workshop to be clinically useful?	Resident survey	Professionalism, interpersonal skills and communication, patient care	Chief resident	
Is this workshop effective in enhancing the resident's experience of being a physician?	Reflective learning: "I can recall a specific clinical encounter in which I thought about something we discussed in the Poetry Workshop."		Dr. R.	

Comments:

Fig. 3. *Sample CEPI page, clinical inpatient service.*

Component: Elmhurst Hospice Service
Category: Clinical
Setting: Inpatient wards
Faculty: Hospice faculty
Description Senior residents manage patients admitted to the Hospice service, under the supervision of faculty of the Department of Ambulatory Care.
Competencies: All

Question	Assessment	Competency	Personnel	Priority
Do residents find this rotation to be clinically useful?	Resident survey	All	Chief resident	
Is there a proper balance between service and learning?				
Is the level of supervision appropriate?	Assessment of resident's mastery of end-of-life palliative care, assessed by Board performance, in-service exam, or patient outcomes.			
At the conclusion of this rotation, does the resident feel comfortable managing palliative care patients at the end of life?				
Is this an effective modality for learning end-of-life care?			Hospice faculty	
Does this rotation have an impact on the resident's professional development?	Reflective learning: "Can you recall a particular experience you had in this rotation that was important to you?"	Professionalism		

Comments:

of patients with this condition, concern arose over the programmatic value of this rotation, especially given the conflicting demands for residents' time. The CEPI approach was applied to address these issues. A resident survey was designed, asking residents about their views of the clinical value of the rotation, their perception of the balance between service demands and learning experiences, and their opinions about the role of the experience in their professional development. The residents' responses could then be analyzed both as a parallel to Dr. P.'s subjective assessment of each resident's mastery of the management of patients in this clinical setting, as well as the counterpart of an objective assessment of their synthesis of the clinical content. In this way, a comprehensive picture of the competency-based programmatic value of this rotation could be drawn, resulting in a refinement and redirection of its learning objectives and curricular goals. To bring the process full circle, the residents' subjective and objective responses to this curriculum refinement and redirection could then be assessed.

Case 3: Evaluative

Consistent with the ACGME's recommendation that formal resident evaluations be collected from professional staff members other than physicians, we developed an evaluative instrument in which ward nurses provided feedback on residents' performance in the competencies of *professionalism*, *systems-based practice*, and *interpersonal skills and communication*. Recognizing, however, that gathering data was easier than ensuring that the data contributed in a meaningful way to outcomes-based resident assessment, we endeavored to address this problem by the CEPI approach. In order to approach the question of whether or not the nurses' evaluations were adding new information about residents' performance, we compared, for each resident, the nurses' assessments of these competencies with that of other evaluators (e.g., attending physicians). We also looked for external measures of the attainment of these competencies (i.e., performance on a clinical evaluation exercise [mini-CEX] and summative scores submitted for each resident to the American Board of Internal Medicine) to correlate with the scores given by the nurses. Further, we looked to demonstrate the programmatic value of the process of nurse evaluation by examining its role in improving the quality of interpersonal and professional interactions between residents and nurses. By this approach, a comprehensive view of the overall programmatic value of instituting these evaluations was obtained.

Discussion

With the public's increasing concern with issues such as medical errors (5), patient safety (6), physician accountability and professionalism (7, 8), physician communication skills (9, 10), certification and licensure, and the overall quality and value of medical care (11), closer scrutiny has been given to the role and quality of medical training and education (2). The ACGME's elucidation of the six core competencies has helped us to define the qualities that comprise the effective physician, while the outcome project (see *Background*, above) has provided a framework for assessing and assuring the success of the training and education process. How exactly to apply these concepts to individual residents and programs, however, has remained a subject of debate among medical educators (12–14). The process described in this report provides one strategy that we have found to be useful. Specifically, we produced a 76-page compendium of 301 questions, which has provided us with a handy, portable document that can be disseminated widely to relevant personnel, including clinical and didactic faculty, residents at each training level, other members of the health care team, and administrators, as a means of collecting input and feedback as to the goals and directions of the program. It thus yields both a *blueprint* of where the program is, as well as a *roadmap* of the directions the program needs to go. It provides a mechanism for the coordinated and comprehensive assessment of diverse program elements.

As illustrated in the examples given above, this multi-step process has a number of strengths. It allows for the concurrent assessment of content- and process-based features with outcomes-based features of each programmatic learning element. It enables us to simultaneously assess a learning element's outcome (demonstration of competency-based effectiveness) and its programmatic value. It integrates the assessment of the cognitive aspects of a programmatic element with its clinical aspects, and it integrates the input of evaluators at various levels. It aids in identifying clinical elements that entail undue or excessive "service demands" and it facilitates the identification of the clinical learning environments where specific elements of learning may occur. Inasmuch as each question is applicable to each of the three years of training, it facilitates a coordinated, systematic evaluation of the progress of learning over the course of the program. In addition, it has the benefit of orienting faculty members to an evidence-based research mode of thinking and teaching.

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Resident as Teacher:

The Mount Sinai Experience and a Review of the Literature

Lisa D. Bensinger, M.D.[1], Yasmin S. Meah, M.D.[2], and Lawrence G. Smith, M.D.[3]

Abstract

Residents play a pivotal role in the education of medical students and junior house staff but are rarely provided with the tools to help them teach effectively. Residents value their roles as teachers and desire training programs in teaching skills. Teaching skills courses for residents have been shown to improve residents' self-confidence and self-assessed use of effective teaching behaviors. They have also been shown to improve residents' evaluations by students.

The Institute for Medical Education at the Mount Sinai School of Medicine has developed a successful, multidisciplinary curriculum to improve the teaching and leadership skills of all of our residents at the Mount Sinai Hospital and its affiliate institutions. The Resident Teaching Development Program (RTDP) has already been implemented in the departments of Medicine, Surgery, Pediatrics, Psychiatry, and Obstetrics and Gynecology. This adaptable, seven-hour curriculum has been well received by residents and faculty.

We are currently evaluating the effects of the program on residents' confidence and use of learned skills. And we are working to expand this program to every department and to create innovative means of measuring resident competency in teaching and its ultimate effect on student learning.

Key Words: Teaching, internship, residency, teaching/methods, medical education, curriculum.

Introduction

Teaching is an integral role of the practicing physician regardless of career path or specialty. Teaching responsibilities begin early in medical education, but the most dramatic shift from learner to teacher occurs during the transition from internship to residency. Many studies have shown that residents are often the primary teachers of medical students and junior house staff (1 – 4) and spend as much as 20 – 25% of their time teaching (3). Residents also commonly teach entire teams of learners at different levels of training and in varied settings. The required skills are difficult to master, even for seasoned teachers. Until recently, most residents were expected to fulfill their teaching responsibilities with little formal instruction despite their critical roles as educators (5, 6).

The purpose of this article is twofold: To review the importance of teaching skills curricula for residents, often referred to as Resident-as-Teacher (RAT) programs, their emergence over time, and their current status in graduate medical education. And to describe the Resident Teaching Development Program (RTDP), an actively expanding, multi-disciplinary curriculum for all residents at the Mount Sinai School of Medicine and its affiliate hospitals.

The Evolution of Resident-as-Teacher Programs

Resident-as-teacher programs began to emerge in the 1960s and 1970s, but were quite rare until the 1990s (7, 8). Medical educators began to develop resident teaching skills curricula, in part, in response to trainee claims of a significant void in residency training (5). Multiple studies conducted in various specialties confirm that in spite of intense time pressures, residents enjoy teaching and consider it one of their important roles (9 – 12). Many residents agree that teaching improves their clinical knowledge and skills and encourages their efforts at self-directed learning (9, 11, 12). The same studies reported that residents' attitudes towards teaching and their levels of confidence af-

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[1]Assistant Professor of Medicine, [2]Instructor of Medicine, and [3]Professor of Medicine and Dean for Medical Education, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Lisa D. Bensinger, M.D., Box 1087, Mount Sinai Medical Center, One East 100th Street, New York, NY 10029.

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fected their self-rated and/or student-rated teaching effectiveness. Educational literature routinely demonstrates that residents would prefer to spend even more time teaching than they already do (10, 11, 13, 14), but feel hindered by multiple factors. Commonly reported barriers to teaching are lack of time, poor confidence in their teaching skills and clinical knowledge, and insufficient training in effective teaching methods (13, 14). In a 1995 study, Yedidia et al. (13) provided powerful examples of internal medicine residents' conflicts about teaching, through a qualitative study that assessed residents' attitudes towards their teaching and leadership roles. Residents expressed difficulties in teaching, supervising and nurturing students and junior house staff during a time when they themselves had the same needs, often felt inadequate, and needed to prioritize teaching with caring for acutely ill patients. Given these possible barriers to effective teaching, it is not surprising that residents rated themselves better as clinicians than as teachers in a study from 2000 (10).

Despite their significant teaching roles, several studies have demonstrated gaps in residents' teaching skills (11, 15, 16). Greenberg et al. (11) reported in 1984 that early data from videotapes showed residents using mostly lecture-style teaching, with little emphasis on teaching problem-solving skills. Morrison and Hafler (15) cited similar data in a 2000 review, which reported that residents rarely used feedback and they questioned learners, demonstrated techniques and procedures, and referenced literature only minimally (16).

Medical accreditation agencies now formally support the need for training in teaching skills in residency programs. The American Council for Graduate Medical Education (ACGME) (17) agrees that teaching is a key part of resident training and has included the teaching of students and other health care professionals as part of the core competency, practice based learning and improvement (PBL). Most resident teaching skills courses actually address multiple competency requirements beyond PBL. The Liaison Committee on Medical Education (LCME) also requires teaching competency for residents and mandates that residents who teach medical students must be "prepared for their roles as teachers and evaluators of medical students" (18).

Many residency program directors have responded to the need for teaching skills instruction. According to a 2001 survey (6) of residency program directors and graduate medical education leaders, approximately 55% of residency programs now offer formal teaching skills training to their residents. The survey by Morrison et al. (6) identifies the percentage of programs offering teaching skills instruction by specialty: medicine-pediatrics (88%), pediatrics (80%), internal medicine (65%), psychiatry (62%), family practice (52%), obstetrics & gynecology (38%) and surgery (31%). This is in contrast to a 1993 survey (5) of internal medicine residency programs, which reported that only 20% of the programs had teaching skills curricula.

This large-scale response to the need for training in teaching skills has resulted in a variety of programs for residents. Some programs are multidisciplinary and overseen by the office of Graduate Medical Education (GME) of an institution, while most are designed and implemented by individual departments (6). Programs have widely variable formats, ranging from brief, hour-long workshops to full-day retreats and even elective rotations (15). If one combines data from all residency programs that offer RAT courses, residents now receive a mean of 11.5 total hours of teaching skills instruction during their training (6). The most commonly used formats for these course include lectures and workshops.

Do Resident-as-Teacher Programs Work?

A recent review by Wamsley et al. (19) on the effectiveness of resident-as-teacher programs reports that teaching courses improve confidence in teaching and self-reported use of teaching behaviors. Resident-as-teacher programs are also linked to improved student evaluations of residents' teaching effectiveness (19). Some studies using Objective Structured Teaching Examinations (OSTEs) show more objective improvement of teaching skills.

There have been several studies evaluating resident teaching skills courses. One challenge to evaluating the effectiveness of such courses is that the formats are often extremely variable. Another is that many programs are taught using small group formats and, therefore, are not powered to measure significant changes in self-reported or learner-evaluated teaching effectiveness. Finally, measuring outcomes can be a complex matter. The goal of most resident teaching skills courses is to improve the teaching skills of the residents who attend. However, the true endpoint is enhanced learning of students and junior house staff and, ultimately, improved patient care by those learners. Measuring these outcomes can be quite challenging, and there are many confounding factors that make analysis of the data difficult.

Therefore, many studies of the outcomes of resident-as-teacher programs have used resident self-assessments of improvement in confidence and skill acquisition. Most of these studies show a positive effect on residents' self-ratings of their teaching skills after the interventions (19–21). Although confidence in teaching skills is not evidence of effective teaching skill, Greenberg et al. (11) linked increased resident confidence in teaching to their perceptions that they could communicate ideas more effectively and feel more comfortable when confronted with profound decisions. Those residents also felt that they received more positive, unsolicited feedback and were more willing to provide feedback.

Other studies have targeted student evaluations of residents as the outcome measure of their teaching courses. Litzelman et al. (22) added medical student evaluations of residents to self-reported pre- and post-assessments of teaching after a weekend teaching skills retreat. They demonstrated improved evaluation of skills in 3 out of 7 domains of teaching and improved self-evaluation in all 7 domains. Spickard et al. (23) and Wipf et al. (24) both demonstrated improved learner evaluations in controlled studies after 3- and 6-hour interventions, respectively.

Educators are now striving to demonstrate direct effects of curricular interventions and obtain more objective evidence of competency. These goals have driven the development of more objective measures of improvement in residents' teaching skills, such as the Objective Structured Teaching Examinations (OSTEs). OSTEs are comprised of multiple skills stations using "standardized students," where residents are evaluated on specific teaching skills by a trained evaluator. An early randomized, controlled trial (25) showed little difference between intervention and control groups. However, more recent studies have reported encouraging data. Morrison et al. (26), in a randomized, controlled study, demonstrated a 22.3% improvement in mean overall OSTE scores of residents compared to pre-test scores, while the control group showed no change. OSTEs have potential to be reliable and valid measures of residents' competence as teachers (27, 28). They represent progress in the goal of measuring direct outcomes of teaching skills courses for residents and faculty.

Some studies have evaluated the effects of teaching courses over time, and most show some decline according to residents' self-assessment or based on more objective analysis (20). These results support the need for "refresher courses" or further training, but data on longitudinal training is lacking. Further research is also needed to determine the most effective content, format, and length of resident teaching courses (19).

The Resident Teaching Development Program at Mount Sinai Hospital

In 2001, The Institute for Medical Education (IME) at the Mount Sinai School of Medicine created the Resident Teaching Development Program (RTDP). This seven-hour, multidisciplinary course was one of the first faculty development programs created by the IME to address of the critical role of residents as medical educators in our institution. The goal of the teaching program is to develop the teaching and leadership skills of all residents who teach medical students at the Mount Sinai School of Medicine, for the purpose of improving the quality of clinical teaching at the Mount Sinai Hospital (MSH) and its affiliates.

To design the program, we reviewed existing literature on teaching skills instruction, examined what other institutions were doing, consulted with educators, and conducted a needs assessment survey. Although the data from resident-as-teacher (RAT) course outcomes provides few hints as to ideal content and format of courses, educational theory and faculty development literature cited features of successful teaching skills programs. For example, adult learning theory, as described by Knowles and others (29), guided much of our course development. Therefore, we structured our course to include active learning and opportunities for practice (e.g., review of videos, role playing, brainstorming), integration of the residents' own experiences, feedback on their use of teaching behaviors, and problem-solving activities (Table 1). Self-directed learning is also encouraged by requiring residents to self-assess and create individualized teaching goals for themselves.

TABLE 1
Resident-as-Teacher Curriculum Design: Features of Successful Teaching Skills Programs

Provide opportunities for active learning
Draw upon residents' own experiences
Allow for practice of new teaching skills and provide feedback
Encourage self-assessment and goal setting
When teaching theory, apply it to real scenarios
Choose content that is relevant to the residents' needs
Consider a small group discussion format to promote active learning and build relationships
Design a curriculum of reasonable depth and breadth for residents' time constraints
Build in time to discuss problems of confidence and conflicting roles
Focus on problem areas specific to residents: effective use of questioning, giving feedback, teaching problem-solving skills

We also turned to faculty development literature about teaching skills instruction, which has documented successful outcomes. Skeff et al. (30) suggest that successful faculty development programs clearly address the needs of the participants, use a systematic approach, consider the workplace of the teacher, integrate curriculum that emphasizes theory and practice, build relationships between program faculty and participants and among participants, use knowledgeable program faculty, and integrate all of this into the higher institutional organization. We accomplished these goals by using the results of the needs assessment survey to guide content choices deemed relevant by the residents (e.g., giving feedback). We also combined learning theory, its practical applications and time for practice into the design of the course. Using a small group format encourages relationship building, discussion, and active learning. In addition, the course is taught either by trained educators or by physicians who have attended faculty development sessions specifically geared to teaching the course. Many RAT courses are taught by faculty in individual departments who are dedicated teachers but may or may not have had formal training. Lastly, with support from both the IME and the medical school, we created a core curriculum for all residents, which provided standardization of teaching. We believe this centralization of the curriculum to be key to the success of the program. The more common, autonomous, department-based approach to curriculum development makes it difficult to standardize and evaluate the outcomes of the courses.

Resident-as-teacher literature helped to guide curriculum development as well. We know from studies mentioned above that residents lack confidence in their clinical knowledge and teaching skills, feel conflicted about their primary responsibilities and are under extreme time pressures. Therefore, we created a fairly compact yet comprehensive curriculum that can be taught in one full day or multiple shorter sessions. During the course, we spend time discussing solutions to residents' lack of confidence and conflicted roles. We also include specific instruction on asking questions, giving feedback, and teaching problem-solving skills, all of which are cited as deficient in resident teaching.

We then met with program directors and chief residents to make the curriculum adaptable to each specialty. The course has subsequently been modified further based on feedback and evaluation data, and now includes three modules: Setting Goals and Expectations, Teaching Theory and Techniques, and Feedback. Thus far, the RTDP has already been implemented in the departments of Medicine, Surgery, Pediatrics, Psychiatry, and Obstetrics and Gynecology at Mount Sinai Hospital and in various departments at its affiliate hospitals. Only 35% of all programs with resident-as-teacher courses have a multi-specialty curriculum, and the RTDP is one of the few programs nationwide to cater to such a wide range of specialty residencies (6; Table 2).

The effectiveness of the RTDP was initially evaluated using pre- and post-course questionnaires to assess residents' self-evaluated confidence and usage of specific skills, and a course evaluation. Preliminary results are encouraging; however, complete data is forthcoming. We are currently planning to develop OSTEs to objectively evaluate residents' competence as teachers.

Soon after implementation of the RTDP, there was a surge in interest from program directors and faculty in other MSH and affiliate departments who were not yet participating. There are approximately 60 departments that train residents at MSH and more than 12 affiliate hospitals. We had a limited number of faculty, resources, and time to teach the curriculum in this many departments. To do so, we created a dissemination program entitled "Teach the Teacher." This 2-day course teaches faculty the content and structure of the RTDP so that they can implement and sustain the course in their own departments. This program was piloted in February 2004 with 13 faculty from 7 specialties, and in 6 affiliate hospitals. We plan to continue Teach the Teacher yearly and build a cadre of educators in the Mount Sinai community who are dedicated to improving residents' teaching skills.

Future Plans

As the importance of teaching instruction for residents and faculty continues to gain recognition, resident-as-teacher courses will probably be given more time in the curriculum of residency programs. Many more resources are now available to faculty

TABLE 2
Unique Aspects of the Resident Teaching Development Program (RTDP) at Mount Sinai Hospital

Has a flexible format: can be taught in one day or multiple seminars
Was designed by physicians with educational training
Core curriculum provides for standardization of teaching
Curriculum is adaptable to any specialty and has been successfully implemented in all major departments
Each specialty department contributed case examples, role plays and issues specific to their fields
Has been disseminated widely using a faculty development "Teach the Teacher" program

and program directors to learn how to teach RAT courses for their own residents. Research will help us provide residents with the most effective content and teaching formats. As hospital stays shorten, residents have even less time to teach. In this setting, teaching skills instruction may become even more valuable for residents, but we need to learn the most efficient and effective means of helping residents teach (31). For example, we need to understand which teaching techniques work best for residents, what degree of training is necessary (single interventions vs. longitudinal training programs), and how to effectively motivate residents to teach despite their time pressures and intense work environment (32). Educational research should also help elucidate the most direct and standardized means of evaluating these programs, so that we can document competency in this critical skill.

Residents dedicate a great deal of time to teaching students and colleagues, and they should be supported in this endeavor. Residents want guidance and training for both their acquisition of knowledge and their teaching activities. We should provide them with the best guidance and training possible.

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Nurse-Practitioner-Led Home Care Curriculum for Third-Year Medical Students

Marina Burke, R.N., A.N.P.[1], and Lawrence G. Smith, M.D.[2]

Abstract

Recent data have shown that medical students do not receive adequate exposure to the practice of home care. The number of homebound people is expected to increase, and health care services for these patients will need to expand. A one-week didactic and clinical curriculum was designed and implemented by four nurse practitioners in the Visiting Doctors Program, to provide home care exposure to medical students. The program stresses the medical, psychosocial and palliative aspects of patient care. The students evaluated both the nurse practitioners and the program favorably, using a five-point Likert scale. Role modeling and professionalism were noted to be of value to the students, and bear further study in the context of medical school curricula for home care.

Key Words: Home care services, education, medical students, nurse practitioners, palliative care, patient care, curriculum.

Introduction

The need to provide health care services for homebound, chronically ill and dying persons is expected to increase in the coming years, as the life expectancy of the U.S. population continues to grow (1–4). Management of chronically ill patients is largely palliative, in that it emphasizes relief from pain, affirms life and accepts death as a normal process. Thus, it differs from the more diagnostic/curative medical management taught in medical schools and practiced in traditional clinical settings. As a result, medical students and residents have had limited exposure to palliative care theory and practice. The importance of palliative care approaches for both chronic and terminal conditions of the elderly has been well documented. Yet terminally ill patients frequently die in severe pain, and are often subject to invasive testing against their wishes (5, 6). Although medical educators are beginning to allot more curricular time to rotations in ambulatory settings (7–10), only one third of all U.S. medical schools include home care training in their curricula and fewer than 25% of internal medicine residencies include a housecall experience (11).

There is also a growing realization that medical training needs to place more emphasis on the psychosocial aspects of care. This is evident in the joint American Board of Medical Specialties (ABMS) and Accreditation Council for Graduate Medical Education (ACGME) initiative that defines competency in terms not only of medical knowledge, but also of patient-centered "domains" such as patient care, professionalism and systems-based practice (12). Role models for these patient-centered competencies may not be as readily encountered among physicians practicing in traditional medical settings as they are among nurses practicing in the home care setting. This is particularly true of nurse practitioners (NPs)—registered nurses with master's level training in medicine—who care for homebound patients in several programs across the country (13–20). The training of nurse practitioners, all of whom are also trained as registered nurses, emphasizes proficiency in understanding the psychosocial aspects of illness, as well as the value of family dynamics within the setting of illness (21, 22). Moreover, these nurses are skilled in counseling patients and families confronted with the anxieties and problems associated with chronic and palliative conditions (23–25).

With these considerations in mind, and understanding that although home care services are delivered by nurses, physicians are ultimately responsible (26), the NPs in the Mount Sinai School of Medicine Visiting Doctors Program designed and implemented a home care curriculum for medical students and residents in 2002. Since 2002, this rotation has been required for all third-year medical students. The purpose of this article is to describe the historical development of the program, outline the structure of the clinical curriculum, and report the results of students' evaluations of the curriculum.

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[1]Visiting Doctors Program, and [2]Dean for Medical Education and Professor of Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Marina Burke, Box 1216, Mount Sinai Medical Center, One East 100th Street, New York, NY 10029; email: marina.burke@msnyuhealth.org

Historical Background

Three residents in the Department of Medicine started the Mount Sinai School of Medicine Visiting Doctors Program in 1997. They began by providing comprehensive primary and palliative care to elderly homebound patients. These physicians were motivated not only by an obvious need for such services in the community, but also by the desire to rekindle the sense of altruism, humanism, and patient advocacy which they felt had been more evident in the earlier years of their medical education.

A majority of the elderly homebound population suffer from multiple chronic conditions, such as cognitive impairment, congestive heart failure, severe osteoarthritis and previous stroke. Because of their advanced age and debilitation, most of these patients and their families prefer that medical and nursing care focus on maximizing cognitive and physical functioning in the home setting. This approach is essentially palliative and emphasizes the relief of symptoms, rather than cure, and the use of resources to maximize patient function. A minority of this patient population consists of terminally ill patients requiring traditional, intensive palliative care. These patients are managed in coordination with the Palliative Care Consult Service of the Mount Sinai Hospital. The Visiting Doctors Program works closely with the consult service, identifying and hospitalizing patients whose symptom burden cannot be relieved with home therapies.

In 1999, four NPs joined the program and developed their own independent panels of homebound patients. The program grew steadily; by the beginning of 2004 it was staffed by four NPs, nine physicians, two registered nurses and a social worker, who together provided coordinated care to approximately 750 patients.

As indicated above, the nurse practitioners designed the original home care curriculum in 2002. Since then, all third-year medical students at the Mount Sinai School of Medicine have spent a one-week rotation in the Visiting Doctors Program. The program also serves as a required rotation for all second-year medical residents and as an elective rotation for many trainees, including medical students, residents in specialties other than internal medicine, and trainees from other institutions.

Structure of the Program

In 2002, the four NPs designed a formal didactic and clinical curriculum for third-year medical students, as part of the medical school's integrated medicine and geriatrics clerkship. This curriculum was developed in response to student feedback to the prior less-structured programs for the third-year students. It was felt that a more-structured, clinically intensive curriculum of four consecutive days would have a greater educational impact. The goals of the program were as follows:

1. To appreciate the medical and nursing needs of homebound, elderly, chronically ill and dying patients.
2. To appreciate the importance of an interdisciplinary approach to home care, which includes the ability to call on a variety of health care resources and agencies to ensure optimal patient care.
3. To develop skill in helping homebound dying patients.
4. To appreciate how cultural, family, and socioeconomic factors influence the delivery of care to homebound persons.

A specific objective was to determine the effectiveness of the nurse practitioner group in helping the students achieve the stated goals. This was conducted by giving participating students the opportunity to evaluate both the program and the faculty.

Didactic Curriculum

Four lectures were given each week on relevant geriatric topics. All the lectures were delivered by the NPs who had developed the curriculum and who conducted the home visits. The lecture topics were as follows:

Wound care. Following presentation of the basic principles of wound pathology, the etiology, diagnosis and management of commonly encountered wounds in homebound individuals were discussed. These discussions were supported by the week's clinical cases. The value of familiarizing family and caregivers with the performance of daily wound care was stressed.

Depression, delirium and dementia. Basic definitions of the syndromes were discussed within the context of a prepared learning case module. Differential diagnosis between the three syndromes was explored in three separate cases. Additionally, each case was discussed as if the patient had been homebound, with emphasis on how diagnosis and management would have differed from that provided in a clinic or hospital setting.

Advance directives and palliative care in the home. Advance care planning and palliative care were discussed, using the program's case studies. Discussion centered on the challenges of patient and family education concerning complex medical decisions, e.g., partnering with families in the decision to keep patients at home versus having them hospitalized, or implementing opioid treatment for shortness of breath in a terminal patient whose family was fearful of patient addiction. Specific clinical examples from the week's home visits were discussed.

Complex case studies. A prepared program case study chosen for a particularly complex combination of medical, psychosocial, and economic variables was discussed. The study elucidated the barriers that health care providers face in providing appropriate medical care to cognitively impaired persons. The discussion taught techniques for solving these problems.

Home visits provided ample time for discussion of the topics presented in the didactic phase of the program.

Clinical Curriculum

Students rotated through the program in groups of two or three. Each student was paired with an NP. There was an attempt to pair the student with the same NP for two days. A typical morning would entail visits to 4–6 patients. The patients were usually on the NP's patient panel, and for the most part the visits were routine. New patient visits and urgent visits of NPs to patients of other providers were also made. Students observed as well as participated in the taking of patient histories. History taking on a home visit requires advanced geriatric assessment skills, including assessment of home and environmental safety, social supports, and possible geriatric syndromes. Students initiated the majority of the physical examinations and observed the NP's confirmatory examination when there were abnormal findings. A Spanish translator was included when necessary. Students were also able to observe the NPs' interactions with registered nurses and physician consultants, as well as with hospital support systems, e.g., laboratory and radiology services. And students had the opportunity to observe NPs working with various agencies involved in patients' care.

Although many or even most of the visits could be described as clinically routine, from a psychosocial point of view they were valuable in illustrating problems or conflicts in the areas of caregiver burden, poor understanding of disease processes, family denial of advanced cognitive impairment, and challenges to maintaining patients' optimal personal care. Considerable time was devoted to discussions regarding these issues. The discussions were usually informal and included not only the clinical aspects of particular cases, but also how best to interact with other components of the health care and social service systems involved, to solve the various problems.

Evaluation

At the completion of the rotation, the participating students were given the opportunity to provide anonymous written evaluations of both the curriculum and the faculty, based on the objectives that had been developed for the program. Both the faculty and the curriculum were evaluated on a 5-point Likert scale from 1 (poor) to 5 (excellent). In evaluating the curriculum, students were asked to evaluate both the didactic and home-visit segments. Seventy (70) out of a total of 116 students responded: a response rate of 60%.

The four NP faculty were evaluated on four characteristics: teaching ability, attitudes and sensitivity in dealing with patients, effectiveness as role models, and ability to spark interest and student participation. Of the 70 students who evaluated the didactic and home-visit segments of the program, 56 completed evaluations of teaching ability and 52 rated attitude, role model effectiveness and the ability to spark interest and participation. The results are presented in the Table. (The faculty ratings were averaged for the four NPs.)

More than 75% of the responses ranked both the curriculum and the faculty as "5" or excellent on the Likert scale. Well in excess of 90% ranked both as very good or excellent.

The students were also given the opportunity to provide written comments. Comments were uniformly positive. The following are some examples:

- "I have had few opportunities to witness such genuine sensitivity towards patients."
- "Thank you for showing me so much during just one week."
- "Knowledgeable, inspiring, genuinely concerned about others."
- "Really excellent caregiver."
- "Wonderful at allowing me to be involved in discussions with the patients."
- "A good role model."
- "Excellent at explaining the patients' psychosocial situation and how that impacted the medical care."
- "Provided a very comfortable environment, making the student feel like part of the team immediately. She obviously cares a great deal about her patients and their families, which is crucial to this type of work."
- "Empathizes rather than sympathizing."

Discussion

It is expected that by 2030, 20% of the U.S. population will be older than 65 years of age (15). As a result, most adults are likely to be chronically

TABLE
Nurse-Practitioner Faculty Ratings

Program Segment	No. of Respondents	Likert Rankings				
		1	2	3	4	5
		No. of (%) of Respondents				
Curriculum	70	0 (0)	0 (0)	2 (3)	15 (21)	53 (76)
NP Faculty						
Teaching	56	0 (0)	0 (0)	2 (3)	12 (21)	42 (75)
Attitude	52	0 (0)	0 (0)	1 (1)	7 (13.5)	44 (85)
Role Model	52	0 (0)	0 (0)	3 (6)	9 (17)	40 (76)
Sparked Interest/Participation	52	0 (0)	0 (0)	2 (2.6)	11(20)	39 (77)

ill for several years before they die, and their need for home health care is expected to increase dramatically, especially as life expectancy in the U.S. continues to grow (1, 26). Chronically ill and dying persons have major health care needs, yet are often invisible in traditional medical settings. The reason is that traditional "doctor-centered" medical care focuses on curing illness and prolonging life; relief of suffering is not always emphasized, as it is in "patient-centered" palliative care (27, 28). Many patients with chronic diseases are homebound, and ideally they need homebound palliative care. The evidence is that medical students are not exposed effectively to the practice of home care (26). This student experience was created to address these educational gaps. Evaluation results indicated a high degree of acceptance on the part of the students of all aspects of the program, and suggest that NPs may be effective patient-centered care role models for medical students. Moreover, exposure to home care experiences of this sort is important in terms of the ACGME-endorsed core competencies now required of residency training programs.

The need for improved palliative care education in medical school curricula is being addressed. Currently, however, traditional, doctor-centered, predominantly didactic approaches are in the majority (29). In one recent study, students indicated that palliative care issues have not been sufficiently addressed, and that "instruction and role modeling have been inconsistent" (30). Students need clinical instruction and observational experiences to understand how to begin caring for dying patients.

A strong doctor-patient relationship is arguably crucial in good medical care, and this is especially true in home care. "Doctor-centered attitudes have been shown to be associated with lower patient satisfaction, and may contribute to decreased trust in the doctor-patient relationship" (30). Medical education has recently begun to focus on how to teach aspects of this, particularly given that the prevailing culture of medicine may be more focused on disease mechanisms than on developing this relationship or on patient preferences. Interestingly, training has started to address these issues in the preclinical years, but some studies have found that these interventions can become "overshadowed" by clinical experiences that are doctor- rather than patient-centered (28).

Role modeling is an important, maybe even crucial, part of how and what students learn (9). The kind of role modeling they receive probably helps shape their later practice styles as physicians. Students arguably spend too little time observing how experienced practitioners care for patients. There is evidence to suggest that such exposure helps influence students to adopt a more patient-centered approach to care (30, 31).

The current high specialization in health care requires that all participants be skilled in interdisciplinary team care. This is difficult with home care, because the patient is isolated from the necessary resources (32–34). The students observed, while at patients' homes, how the NPs navigated the various agencies involved in patient care. The "systems-based practice" competency is well addressed in this experience.

Reflective learning may be central to learning in practice-based settings, but it has been undervalued in medical education (35–40). The clinical structure of home care rotations may promote a reflective process not possible in inpatient or outpatient settings. Being physically outside of the medical center both in transit and in the patients' homes provided a neutral and possibly fertile space for better reflection. The structure of the rotation provides this neutral space, where students were surrounded by patients, one NP and family members, instead of the setting of their other rotations, with dozens of medical team members, overhead pages and patients in hospital gowns. This different physical structure and the fact that there was ample time for the student and NP to discuss the visits privately, constituted a unique "informal curriculum." This type of informal curriculum can internalize "new values, attitudes and rationales about what is important in practicing medicine and how to be a good doctor" (28).

Discussions in the rotation exposed the students to different rationales and attitudes than they usually encountered in other rotations. Instead of the medically focused case presentations commonly employed in an inpatient or outpatient setting, in this rotation the medical management of patients was discussed within the context of family dynamics, palliative care choices made in partnership with patients and caregivers, and home safety.

Home care practice tends to build trust and empathy between caregiver and patient. Exposing medical students to this type of care may thus help foster more human relationships between them and their future patients.

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Improving the Adjustment of Educationally Disadvantaged Students to Medical School:

The Summer Enrichment Program

Benjamin Kornitzer, M.D.[1], Edward Ronan, Ph.D.[2], and Mary R. Rifkin, Ph.D.[3]

Abstract

The Summer Enrichment Program (SEP) is a 6-week pre-matriculation program that targets students who may be at an educational disadvantage and/or may have difficulties adjusting to the rigors of medical school. The objective of the current study was to determine whether the SEP (a) eased the transition to the first year of medical school and (b) had an impact on academic performance during the first year of medical school. All students from groups underrepresented in medicine, who had been invited to participate in the SEP, and all Humanities and Medicine Program students who matriculated at Mount Sinai School of Medicine between 1999 and 2003 and were still matriculated during the 2003–2004 academic year were asked to respond to a survey distributed in the spring of 2004. In addition, student academic profiles were reviewed. Responses to the survey indicated that the SEP provided important emotional benefits for those students who chose to attend the program. Virtually all students who had attended had praise for the program and felt that it eased the transition to medical school, helped build confidence and facilitated social connections. In addition, those students from groups underrepresented in medicine who attended the SEP had less academic difficulty (fewer course failures) in their first year of medical school.

Key Words: Underrepresented students, educationally disadvantaged, pre-matriculation program, adjustment to medical school, first-year performance.

Background

Over the past quarter century, several medical schools have developed specialized pre-matriculation programs to improve the academic success of accepted minority students (1–4). In 1970, Mount Sinai School of Medicine (MSSM) developed a novel pre-matriculation Summer Enrichment Program (SEP) for students who are educationally disadvantaged and may have difficulty adjusting to the rigors of medical school. Although originally established for students from groups underrepresented in medicine (URM), the SEP now targets other students who may be at an educational disadvantage in their first year of medical school. In fact, in recent years a large percentage of students attending the SEP have been admitted to the medical school through a special early acceptance program—the Humanities and Medicine (H&M) Program—designed to attract non-science majors to a career in medicine (5). H&M students have participated since 1991.

The SEP focuses on four first-year courses: molecules and cells (an integrated biochemistry, cell biology, and molecular biology course), gross anatomy, histology and physiology. The program does not have formal examinations and does not grade students' performance; however, students take weekly self-graded tests so that they can assess their academic progress. Because attending this summer program may be a financial burden for students who might otherwise seek employment, free housing and a stipend are provided. Participation is totally voluntary.

In the mornings, students attend didactic sessions on topics in biochemistry, taught by a senior faculty member. In the afternoons, they participate in laboratory sessions run by medical school teaching assistants who have already completed the first year curriculum. The laboratory component includes histology, physiology, and gross dissection of the back, thorax, abdomen, and pelvis. These sessions devote the largest blocks of time to first-semester courses (gross anatomy and molecules and cells, and gross anatomy), and a smaller amount of time to second-semester courses (histology and physiology).

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[1] First year internal medicine resident, Massachusetts General Hospital, Boston, MA, [2] Assistant Dean for Academic Affairs, and [3] Director, Humanities and Medicine Program, Department of Medical Education, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Mary R. Rifkin, Ph.D., Box 1623, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

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The purpose of the current study is (a) to determine whether those students participating in the SEP perform better academically in the first year of medical school or have an easier time adjusting to medical school than those who do not participate and (b) to assess the success of the program based on the results of a survey administered to students who have completed the SEP. Both quantitative and qualitative assessments will be presented.

Methods

All URM and H&M students enrolled in MSSM during the 2003–2004 academic year were included in this review. These students were divided into four groups: URM students who had attended the SEP program (n=17), URM students who had not attended the SEP program (n=25), H&M students who had attended the SEP program (n=40), and H&M students who had not attended the SEP program (n=16).

Survey Instrument

In the fall of 2003, a survey instrument was developed by the authors and reviewed by other members of the Institute for Medical Education both informally and as part of research presentation. Using this feedback, the final version was distributed in the spring of 2004. It evaluated: (a) the factors that led students to participate or not participate, (b) subjective factors relating to the transition into medical school, (c) overall ratings of the program and student perceptions of its success, and (d) the academic benefits the program had provided in terms of the four first-year courses discussed above. Finally, students were encouraged to provide written feedback on the program, commenting on their reasons for attending or not attending. Students who attended were also asked to comment on the strengths and weaknesses of the program.

The survey, which was distributed to students via email, used E*value, a web-based survey tool developed by Advanced Informatics (Minneapolis, MN). In the week before the program went on line, students received correspondence explaining the research project. At this time, students were informed that participation was completely voluntary and that all answers would be anonymous. Students were given one month to complete the survey, and all answers were transferred to SPSS v12.0 (Chicago, IL) for data management and analysis.

Measures of Academic Performance

The students' academic files were accessed to determine their undergraduate grade-point averages (GPAs) and Medical College Admission Test (MCAT) scores, and to identify any academic difficulty they had during the first year of medical school, measured by failure rate in four first-year courses (molecules and cells, gross anatomy, histology and physiology). Mean undergraduate GPA and MCAT scores were compared using the t-test.

Results

A total of 92 students were surveyed. Students in all four years of the medical school were represented. Overall, 85.9% of students responded to the survey, with the response rate of the four groups nearly identical (Table 1).

Survey

Attendance Factors. For both URM and H&M students the reason most often cited as "very important" for attending the program (Table 2) was that students believed that attending the SEP would better prepare them for their upcoming medical school courses. The second most important attendance factor reported was that students hoped the program would help them develop confidence. Only a few students said they attended because they had no other summer plans.

Among students who did not attend the SEP, the reasons most often cited as "very important" were that they already had other plans and the fact that they felt confident about being able to make the transition to medical school.

TABLE 1
Comparison of Student Response Rate to Survey

	URM		H&M	
	Attendees	Non-attendees	Attendees	Non-attendees
Total number of students	15	23	39	15
Number of survey responses	14	18	33	14
Survey response rate	93.3%	78.3%	84.6%	93.3%

TABLE 2

Factors Influencing Students' Decision to Attend the SEP: Percent of Students Responding "Very Important" to the Survey Question "How Important Were the Following Factors in Your Decision to Attend the SEP?"

	URM (*n*=14)	H&M (*n*=33)
Thought it would help with coursework	71.4%	81.8%
Would give me confidence to handle transition to medical school	57.1%	75.8%
Stipend helped with expenses	57.1%	48.5%
Would allow me to settle in Aron Hall [dormitory] before med school started	42.9%	51.5%
Would enable me to make friends before med school started	21.4%	27.3%
Had nothing else to do	7.1%	6.1%

Number in parentheses is total number of responses analyzed.

TABLE 3

Factors Helping Transition to Medical School: Percent of Students Responding "Agree Strongly" or "Agree Somewhat" to One or More of the Factors Listed in the Survey Statement, "The SEP Helped My Transition into Medical School in the Following Ways."

	URM (*n*=14)	H&M (*n*=33)
Thought it would help with coursework	71.4%	81.8%
Gaining the needed confidence	85.7%	97.0%
Made the overall transition easier	100%	97.0%
Making friends	100%	93.9%

Number in parentheses is total number of responses analyzed.

Academic Preparation. In terms of academic preparation, students reported that the SEP program best prepared them for first semester courses (Figure). Approximately half of all participants reported that the SEP helped significantly with gross anatomy and molecules and cells, while between 38.3% and 48.9% reported that the SEP program was somewhat helpful in terms of preparing for these courses. A smaller number of students found that the SEP program helped significantly with coursework in the second semester (histology and physiology), while approximately half of respondents reported that the SEP helped somewhat with these courses.

Overall Rating. Of note is the fact that respondents overwhelmingly agreed that attendance in the SEP greatly improved their adjustment to medical school (Table 3). Virtually all students who participated in the SEP reported that the program (a) eased their transition to medical school, (b) helped them build confidence, and (c) helped them establish friendships.

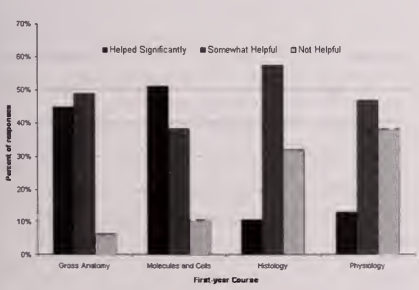

Figure Student Perceptions of Academic Benefit of SEP by Course. Responses to the question "Did attendance in the SEP help you with the following courses?" were analyzed for all students who attended the SEP (both URM and H&M).

Both the written responses and the survey responses indicated that students had a very positive overall experience. Specifically, 85.7% of URM attendees and 87.8% of H&M attendees reported that their expectations of the program were either fully met or mostly met. All URM attendees and 93.9% of H&M attendees felt that they made the right decision by attending. In a similar vein, approximately nine out of ten attendees said they would recommend or highly recommend the program to other students.

Written Feedback

The written feedback was strongly positive, in terms of the major features of the program and why students chose to attend. Virtually all students had praise for the program. Students frequently remarked that the program was a significant confidence booster and improved their adjustment to medical school. In the words of one H&M attendee: "I felt much more confident and enthusiastic about going to medical school. I was able to make the shift in my studying from a humanities mindset to a more scientific mindset.... [The course director] really helped to calm my fears and remind me why I wanted to go to medical school in the first place." Many students also mentioned that the program helped prepare them academically for the challenges of medical school. One URM attendee wrote: "SEP helped me to gain a realistic expectation of what the first year of medical school had in store." Another URM student stated that the SEP was a "great opportunity to get pointers on what materials to use and how to approach the coursework."

Several students thought the real benefit of the program was not so much in providing academic preparation as it was in helping them "emotionally and psychologically feel ready for the experience [of medical school]." Similarly, a number of students described the advantages in forming early friendships for their socialization into medical school. It is also worth noting that even though the course director's name was not mentioned in the survey instrument, twelve attendees specifically mentioned his teaching and mentorship as one of the key benefits of the program. One H&M attendee wrote that the course director was the "key to the SEP program. He not only made it educational but also made sure that every student was well-adjusted to our new environment."

Very few negative or critical comments were returned. Three students suggested that some sort of formal academic enrichment program be offered during the pre-clinical years, and perhaps even between the first and second years, as well. Several non-attendees mentioned the fact that they wanted to take advantage of their last "free" summer before medical school began and also to avoid burnout. This sentiment was well summed up by one non-attendee, who wrote with a certain economy: "1styearislongenough."

First-Year Academic Performance

Among the Humanities and Medicine students, only one student had academic difficulty in year 1, as determined by failure in one or more of the four courses introduced during the SEP (gross anatomy, molecules and cells, histology, physiology). This student had attended the SEP. Because of the small sample number, we could not derive any significant correlation between the failure rate and attendance in the SEP for the H&M students. And the undergraduate GPA of H&M students who chose to attend the SEP did not differ significantly (p>0.5) from the undergraduate GPA of H&M students who chose not to attend the SEP.

Among the URM students, 2 out of 15 (13.3%) students who attended the SEP had course failures in one or more of the four first-year courses mentioned above, while 6 out of 23 (26.1%) students who did not attend the SEP had failures in these courses. While these are striking results, the numbers are too small to allow meaningful statistical analysis by the chi-square method. And the mean undergraduate GPAs and MCAT scores of URM students who chose to attend the SEP (3.11 ± 0.24; 27.7 ± 2.2) were not significantly different (p>0.1 for GPA, p>0.2 for MCAT) from the scores of those who chose not to attend the SEP (3.25 ± 0.24; 27.1 ± 2.0). Thus, failure in first-year courses among these students is unlikely to be correlated with difference in undergraduate GPA or MCAT scores, but may be correlated with attendance in the SEP. Future analyses will have to use a larger sample number to verify this conclusion.

The academic performance of a third group of URM students, those who were not deemed educationally disadvantaged and therefore were not invited to attend the SEP or who were accepted late in the admissions process and therefore were could not attend the SEP, was also analyzed. It is interesting to note that among these students, all of whom were in the late acceptance category, 3 out of 32 (9.4%) had course failures in their first year.

Discussion

Improving the academic success of educationally disadvantaged students is an important challenge that medical schools must address. One method beginning to gain popularity employs prematriculation programs, such as the one described in this study. According to a table published in *Academic Medicine*, 67 of 127 medical schools offer such a program (3). However, little research has been published on the topic, and considering the significant differences in these programs and in medical school curricula in general, it is essential that individual programs be evaluated for the impact they have on participants' academic success.

This study shows that for URM students, the failure rate in one of the four major first-year courses was twice as high for those students not attending the SEP as for those attending the SEP. Attending the SEP thus not only helped these students adjust to their first year of medical school, as judged from the survey responses, but it also led to better academic performance in the first year.

The main limitations of the study were the small size of the study population (convenience sample) and the subjective nature of the survey, even though that is an appropriate method for assessing the impact of the program.

Despite some of the shortcomings that limited the present study, the results obtained appear consistent with previously reported studies, which demonstrated the positive effect such programs have on the first-year academic performance of educationally disadvantaged students. For example, a study published by Ugbolue and colleagues documented a 6-week pre-matriculation program at Boston University School of Medicine (1). Much like the SEP, the Boston University program was voluntary and focused on biochemistry and gross anatomy. Participants in this program had lower failure rates in several first-year courses, and survey results indicated that students had a positive experience with the program. Similar findings were reported for the first year of a new pre-matriculation program at the University of South Florida College of Medicine (4). A study from the Medical College of Georgia examined a pre-matriculation program at that campus designed to provide early academic support to academically disadvantaged students (2). Although the program at the Medical College of Georgia was not able to document any statistically significant difference between the academic performance of attendees and that of non-attendees, more than 90% of attendees reported that the program played an important role in their adjustment to medical school.

Based on the findings of the current study and previous research, it seems that pre-matriculation programs play an important role in improving the academic success of certain educationally disadvantaged students. At Mount Sinai, attendance factors demonstrated that it is the academic component of SEP that attracts participants, but that the benefits extend beyond this realm. Specifically, data from this project indicate that students perceived the program as having a very positive impact on their overall transition to medical school. Key reasons for the SEP's success appear to be (a) the academic preparation it provides for specific courses, (b) the confidence and study skills that it helps the attendees develop, and (c) the important early peer and faculty relationships it cultivates.

Another notable finding from the current study is that first-year course failures among URM students not invited to attend the SEP were limited to those students who were accepted late in the admissions cycle and therefore did not have an opportunity to attend the SEP. It may therefore be worthwhile to consider targeting the admission of educationally disadvantaged students to an earlier point in the admissions cycle. Based on student feedback, it may also be worth considering some type of formal enrichment experience during the school year to complement the materials and study skills introduced over the summer. This approach may be of benefit to both attendees and non-attendees.

Indeed, it is a testament to the success of the SEP that it has been able to achieve its goals while remaining totally voluntary, encompassing a broad range of students from different backgrounds, and allowing participants to monitor their own progress in a non-threatening, grade-free environment. Because producing the SEP requires significant resources and faculty teaching time, maintaining the program is a challenge to the institution. However, considering the positive impact that programs such as the SEP have consistently demonstrated, it is imperative that medical schools continue to invest in this type of initiative, which empowers students to succeed.

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“Writing About Medicine”:

An Exercise in Reflection at Mount Sinai (with Five Samples of Student Writing)

SUZANNE FEIGELSON, M.SC.[1], AND DAVID MULLER, M.D.[2]

Abstract

This paper describes the introduction of a new elective, "Writing About Medicine," into the Mount Sinai School of Medicine (MSSM) curriculum, part of a new trend of developing humanities programs at medical schools. The paper will first survey two exemplary programs at other schools, and discuss their impact on students. It will then detail the development of "Writing About Medicine," including its purpose and format. Finally, it will present focus group data evaluating the course and elaborate on its role in the MSSM educational process. Five samples of student writing follow the discussion.

Key Words: Humanities, narrative medicine, creative writing, medical education, professionalism.

Introduction

The past decade has seen a systematic effort to diagnose, treat, and discharge hospital patients faster than ever. These changes have left physicians or trainees with little or no time to spend at the bedside, developing the skills of empathic care giving. Therefore, medical schools have been searching for new strategies to teach students how to understand patients better and communicate with them more effectively. The study of the humanities, which holds these skills at its core, provides one promising avenue towards this goal. Medical educators have pursued this path in two ways. First, in recent years, students with limited science backgrounds have been admitted to medical schools in greater numbers. Second, some institutions have begun to integrate humanities courses into their basic science curricula (1 – 5).

At the many medical schools where they exist, programs in "humanities and medicine" range in both quality and scale, from humanities-based electives (UMass's "Creative Writing for Medical Students") to programs that use reading and writing as part of the standard curriculum (Northwestern University's second-year course, "The Profession of Medicine"), to Humanities and Medicine or Narrative Medicine Departments (Columbia's "Program in Narrative Medicine," www.narrativemedicine.org). At least 10 institutions have developed these programs or departments, including Northwestern, NYU, Penn State, Columbia, and SUNY Stony Brook.

Although many programs emphasizing patient-centered medical training have established curricula in ethics and "professionalism," this article will focus specifically on the method of utilizing reading and writing to accomplish similar goals. First, we will provide a brief review of two fully developed programs, at SUNY Stony Brook and Columbia. Then, we will describe in detail the elective "Writing About Medicine" at Mount Sinai, and present data evaluating its effectiveness.

Columbia College of Physicians and Surgeons

Established in 1998 by Rita Charon, M.D., "Narrative Medicine" is a method of fostering empathy in care by using reading and writing as tools (6). A "narrative" approach seeks to understand the patient in the broader context of his or her story. This involves soliciting the patient's perception of illness and cultural beliefs, and giving these issues greater emphasis. For example, the social history is taken not simply to establish medical facts (drug

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From [1]Medical Education and [2]the Department of Internal Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Suzanne Feigelson, Mount Sinai School of Medicine, 50 East 98th Street #4F, New York, NY 10029; email: Suzanne.Feigelson@mssm.edu

use, infections, insurance), but also to understand what the illness might mean to the patient.

According to Dr. Charon, a physician who practices medicine without "narrative competence" risks misunderstanding and alienating the patient, fostering ineffective communication and (ultimately) noncompliance. The Program in Narrative Medicine serves to train students from their second year onward in the skills of reflection and communication. Second-year medical students are required to take a half-semester elective humanities course at Columbia College, for credit.

The most transformative phase of Columbia's program lies in the third year. For several weeks during their internal medicine clerkship, randomly selected third-year students are asked to keep notes in a "parallel chart" (6). This serves as a reservoir for the students' subjective experiences with their patients, which are shared in small group settings once a week. Eighty-two percent of participating students said the exercises were beneficial in preparing them for conversations with patients and families. Faculty members concurred that the students were better prepared to interview patients and to assess their needs. Preliminary data show that all the participating students established better connections with their patients and made more coherent case presentations. According to Dr. Charon, reflective writing enables students to review and clarify their experiences and understand the strengths and weaknesses of their care-giving. It also equips them to listen more attentively to their patients' stories, in the hope of forming more effective doctor-patient relationships (6).

Stony Brook University

Stony Brook University introduces its program, "Medicine in Contemporary Society," in the first year of medical school. Students keep journals and receive a grade for their work (7). They also attend 50 hours of small group discussion on the relationship between medicine and other aspects of contemporary culture. The program continues with another 50 hours in the second year, after which students hand in a creative writing project, either a personal or academic essay on a topic in the medical humanities. In each of their third-year clerkships, students are asked to complete writing projects designed by the clerkship directors in collaboration with in-house Humanities and Medicine faculty. Finally, the fourth year offers an optional sub-internship in "Humanism and Medicine" that further integrates journal writing with clinical practice. Stony Brook's objectives for narrative training are to foster skills in recognizing social questions; develop a knowledge base of humanities and social sciences; form attitudes of compassion, curiosity, and collegiality; strengthen analytic skills; improve communication skills; and sharpen learning skills.

"Writing About Medicine" at Mount Sinai

The elective "Writing About Medicine" was started by the authors in an effort to foster reflection among students. Pre-clinical studies can cause students to lose sight of the patient-centered goals that often led them to a career in medicine. The elective, which began with 8 students from the class of 2006 in the winter of their first year, was designed to help students remain connected to the humanistic dimension of medicine. It consisted of seven two-hour meetings, roughly three weeks apart, organized around the following topics: "in'doctor'ination," anatomy, pain, illness, aging, death, and recovery (Table 1). Topics were selected based on those that were most stimulating to students at other institutions with humanities and medicine curricula, according to their program directors. The course was limited to 12 students, a size believed to be most conducive to small-group discussion. Each meeting had four components:

1. **Readings:** Students were assigned readings from a variety of genres, including essays, poems, articles, and short stories.
3. **At-home writing assignments:** For each of the meetings, half of the students were asked to complete a creative writing assignment on the given topic. Students mostly wrote personal essays, but some preferred to write poetry or short fiction. These assignments were handed in to the faculty advisor for review prior to each meeting.
4. **In-class writings:** At the beginning of each meeting, students would write for 20 minutes in response to a question or passage read by the instructor.
5. **Discussions:** To open and support the discussion, students were given the opportunity to read all or part of their in-class writings. The discussion would continue for the first hour, drawing from the in-class writings and the readings, and when the instructor felt it was appropriate, he would hand back a take-home writing to the author to read on the spot. The class would then give the writer feedback on both content and form.

Following the seven sessions, focus groups were conducted by an independent administrator to glean feedback from the participants. Based on this

TABLE 1
Course Syllabus for Writing about Medicine I

Subject	Reading	Writing
In'doctor'ination	1. Rita Charon, "To Build a Case: Medical Histories as Traditions in Conflict" 2. Elspeth Cameron Ritchie, "Language Barrier" from *Hospital Sketchbook: Life on the Ward Through an Intern's Eyes* 3. Peri Klass, "Learning the Language" 4. Two compositions by Mount Sinai residents	In class: Where are you right now? Start with your immediate physical surroundings and see where it takes you.
Anatomy	1. Dannie Abse, "Carnal Knowledge" 2. CK Williams, "Dissections" 3. Peri Klass, excerpt from *A Not Entirely Benign Procedure: Four Years as a Medical Student*	At home: Compose a letter to your cadaver, explaining what you did and why you did it. In class: Pick someone you care about and convince him/her either to donate his/her body to science or not to.
Physical Pain	1. Elaine Scarry, "Introduction" from *The Body in Pain: The Making and Unmaking of the World* 2. Fanny Burney's letter and Richard Seltzer's critique, from *Raising the Dead: A Doctor's Encounter with His Own Mortality*	At home: Describe an experience of physical pain, either yours or someone else's. In class: Describe an emotionally painful experience.
Illness	1. Virginia Woolf, *On Being Ill* 2. William Carlos Williams, "Jean Biecke" 3. Lorrie Moore, "People Like That Are the Only People Here"	At home: Describe a time when you experienced illness, either yours or someone else's. In class: You get a letter notifying you that you tested positive for hepatitis C. Write your reaction.
Aging	1. Elanor Cooney, "Death in Slow Motion" 2. William Dean Howells, "Eighty Years After"	At home: Describe aging from the point of view of someone who has aged. In class: Which is more difficult: physical or mental decline? Select one and write about it.
Death	1. Ernest Hemingway, "A Natural History of the Dead" 2. C.S. Lewis, *A Grief Observed*	At home: Write about death. In class: React to an excerpt (read aloud) from C.S. Lewis.
Recovery	Jack London, "Love of Life" from *Stories for Boys*	At home: Describe a recovery, either medical or non-medical. In class: React to an excerpt (read aloud) from Jack London.

data, the authors ascertained students' original expectations, their personal "cost/benefit" analysis of the experience, and their ideas of how the course impacted their education (Table 2).

Expectations of the course ranged from professional ("I wanted a 360 degree view of medicine") to personal ("not to go insane") to intellectual ("I really missed the intellectual and creative culture at college"). As one student said, "I wanted to think about med school things in less of a med school way." The cost/benefit analysis reflected an overwhelming benefit and almost no cost. Students

TABLE 2
Focus Group Data

Expectations	Outcomes	Impact of the Course
—Establishing a connection with like-minded classmates —Gaining tools for reflection —Rekindling humanities interests pursued in undergraduate training —Having the opportunity and discipline to write —Improving writing skills	—Looked forward to class time —Felt happier in medical school —Felt more satisfied with medical education —Felt more confident in ability to be a good doctor —Course was emotionally challenging, but not distressing —Positive contact with faculty	—Students imagined they were less disillusioned with medicine than they would have been without the course —Students found that reflection and creativity enriched their training beyond what the standard first-year curriculum provided —At the end of the year, students felt a greater connection to their classmates than they would have without the course

said "it required energy" and "it was emotionally challenging at times...but that was good." "I think the fact that we all got up at 7 AM to go to the elective—on a couple of separate occasions...and stayed late once, [suggests that] we were definitely into it." "It was a place where you felt like somebody was watching out for you and cared for you," another added. Students said they felt happier, more satisfied with their education, better about Mount Sinai, and more confident. When asked, students could not think of any other way they would have rather spent their time, including sleeping, eating, or studying.

The course has continued into the second and third years, following a similar schedule and format in each term. All of the students participating in the first-year course continued into the second and third years. The course has also been offered to the classes of 2007 and 2008. Twelve students enrolled from the class of 2007. This class made minor adjustments to the syllabus and continued with all 12 students into their second year. The course will be offered to the class of 2008 beginning in the winter of their first year.

Discussion and Future Directions

"Writing About Medicine" is Mount Sinai's first effort to train its students in reflection and "narrative competence" by using reading and writing as its primary tools, as Columbia and Stony Brook have done. Although the methods of "Writing About Medicine" are unique within the Mount Sinai curriculum, its educational objectives are consistent with other efforts of the medical center to train humanistic doctors. Paramount among these is "The Art and Science of Medicine," spanning the first two years, which includes weekly lectures, small group discussions on ethics, patient-centered care and other non-biological topics within medicine, as well as physical diagnosis training and introduction to the clinical encounter. Course offerings during the third-year intersession and fourth-year electives include reading and discussion groups that explore students' reactions to medical training. The Visiting Doctors program for internal medicine residents also devotes several sessions to this type of activity. In addition, student groups have organized lecture series dedicated to humanism in medicine.

A unique expression of Mount Sinai's commitment to humanism in medicine is its program "Humanities and Medicine," which provides a path to medical school offering maximum flexibility in the undergraduate years for students to explore their interests in humanities and social sciences without having to take the MCAT or complete the standard premed course load (8). The program has been remarkably successful in recruiting diverse, nontraditional premed students. Columbia and Stony Brook, while more advanced in the development of humanities and medicine curricula at their institutions, do not have comparable programs that solicit and nurture humanities students in the undergraduate years. "Writing About Medicine" has the potential to become an excellent complement to the Humanities and Medicine program, by reinforcing its values once graduates of the program have begun their medical training. For students with more traditional premed backgrounds, the course helps to enhance verbal communication skills and provides training in reflective practice.

Frederic Hafferty, in "The Hidden Curriculum," writes that students learn the core values of medicine not in lecture halls or on medical rounds, but in more informal, unsupervised settings where reflection takes place. By allowing students the opportunity to reflect on their shared experiences in the presence of a faculty member, "Writing About Medicine" presents an opportunity to integrate this more personal realm into medical students' formal training (9).

To build on the positive effects of "Writing About Medicine," we will continue to develop forums that include reading and writing for trainees at every level of medical education. In the long run, our goal is to design a curriculum similar to those offered by Columbia, Stony Brook, and other institutions, a curriculum that will span the four years of medical education and involve the entire student body. We also plan to offer programs for the rest of the medical community in close collaboration with the Humanities and Medicine program.

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Phone Call

Judith Goldfinger
MSSM '06

They had been on the phone for nearly an hour, and her reserves of kindness were nearly dried up.

The woman was lying on the floor, sometimes on her stomach, sometimes on her back. She began the conversation with the phone in her right hand. When that arm and elbow got stiff, she switched hands. Soon enough, her left ear reddened from the pressure of the receiver, and she switched back. As the call reached the hour mark, she tried to calculate how many times she had switched the phone from ear to ear, and she realized that she could not get more precise than an estimate of four to six.

"Four to six, fooor too seeeeks," the woman repeated over and over in her mind until the words had lost all meaning, like an object whose lines begin to blur when stared at for too long.

She mentally reviewed the call. Male caller, undergraduate, stressed over his grade on a recent test. The caller was feeling overwhelmed and anonymous in the large college. He was having trouble making friends and he missed his long-distance girlfriend. This was a typical call, a variation on a theme that she had visited and revisited numerous times. Of course, for the caller these problems were intensely personal, special, and even unique.

The woman had played the role of counselor well on this call, she decided, as she switched the phone to her other ear. Was that ear switch number five or seven? Back to the call: plenty of non-verbals, "uh-huh," "hmmm," and "yeah." She had validated every feeling he expressed. "It is totally understandable for you to feel overwhelmed. The workload can be really considerable." "It can be really hard when you are here, and your girlfriend is so far away, and you just really want to be with her." "It sounds like you are feeling really alone right now, which can be really difficult." "It is always hard to come to a new place and meet new people."

The woman was proud of her performance. She had empathized and commiserated. She suggested clubs related to his interests, as potential meeting places for new friends. She recommended peer tutoring and potentially helpful meetings with deans. She gave him phone numbers and email addresses, never pushing, always just suggesting, even as she emphasized how vital these measures could be. And he took them all, wrote the numbers and email addresses somewhere on his side of the phone line, and then repeated them back to her to make sure he had them right. It was very rewarding for the woman, the counselor, that he did this. So many times she had tried to give a phone number to other callers, perhaps had spent a minute or so explaining how useful the resource could be, only to hear these callers say, "Oh, that's OK, I don't really think I need *that*." Or, "Well, not *now*, if I decide that I need it, I guess I can just call back at a different time."

This caller was different. She felt him responding to her attempts at sincerity, felt the rapport grow between them.

Then the man said, "I'm sorry." And she was momentarily taken aback, confused, thought perhaps she had said aloud, "Six or eight," as she switched the phone yet again. And he said, "I feel that I have been taking advantage of your compassion."

The woman thought, this is not compassion. I am the counselor and I am doing what I have been taught, and you are responding to studied words and phrases. You are calling an anonymous and confidential hotline so you can share your thoughts and feelings with someone who does not know your face or story, who is not tired of hearing your grumbling, and who sees you only as you choose to present yourself. This is a forum where I will judge you in my own mind, but you will never know it or even sense it, and you will see me as nonjudgmental.

Then the woman surprised herself and said, "Well actually my ear hurts." The man responded "Um-hmmm" encouragingly, and she could not stop herself from thinking, good non-verbal. She found herself wanting to explain about the worn-out couch and the shag carpet on the floor. She looked around and saw the faded posters tacked on the walls of the small room, for past conferences about domestic violence and eating disorders.

Then the woman realized what she had said, and she amended her complaint. " Not that my ear hurts from listening to you, no, no, just that the actual phone is pressing on my ear, you know?" And the man said "Um-hmmm" again and then he said, "I find that it helps to switch ears."

"I have been doing that," she said. "It does help. Somewhat."

"Or try lifting your eyebrows," he said. "Try doing it in a way that kind of stretches your ears out."

The woman realized that the caller would never know if she, on her side of the phone call, was taking his advice or not. Just as she would never know what the caller was doing with the phone numbers and her advice, whether he followed through.

"I am doing it," she said. "Lifting my eyebrows, I mean. And it is helping. It really is. Really."

"It's a good trick," he said. "I keep doing it. Otherwise your ears fall asleep, which is pretty uncomfortable. And then you can barely even concentrate on what is going on, because you are so conscious of your *ears*. And switching the phone a hundred times is ridiculous."

Yes, she thought, *yes*, exactly. And now she had to regain control of the conversation, reestablish their respective roles. "So when you called tonight, one of the things that you mentioned was that you were lonely, that it is hard for you, because you came from a small high school where everyone knew everyone else. And one of the things that we talked about was you getting involved in clubs or activities on campus to try to meet some new people, and feel more a part of things. And so I gave you some numbers, and you took those numbers, which was really great, because it can be hard, you know, to take the initiative and try to do something for yourself. To try to make things better for yourself. That is really great. And I want you to promise me that you will call. For yourself."

And the woman realized that she desperately needed to know that he would call one of those numbers. She knew that she had another hour on the hotline, and then she would go home and go to sleep. In the morning, she would wake up and be one of the thousands of nameless people on the large college campus. She would spend the whole day thinking about a lonely man who thought her compassionate and had been, for at least a moment, truly concerned about her ears.

The Tale that We Spun

LAURA PILAR GELFMAN
MSSM '06

I EXPERIENCED HIS ILLNESS over the telephone. The diagnosis, the symptoms, the treatment and eventually his death, all over the telephone over a three-year period, one twelve-year-old confiding in another. Many days it was more than I could bear, but most days I had little capacity to connect the symptoms and the treatments with the prognosis. I did not know that it was a bad sign when one of his lungs filled with fluid, or the day when he began another round of an experimental chemotherapy, or when he began spending less and less time in Miami and more and more time in Houston getting treatments. I did not realize how willingly I believed in his stories and I did not realize how much he needed me to believe in the myth that he had created for me. It was a story that he wove for me each day and each day a story that I digested. He needed me to believe that he was going to be okay, just as I needed to believe that I could help make him okay. I learned the language of his illness with a vocabulary of a twelve-year-old.

As the treatments continued and the days he spent in school became fewer, I came to rely on his voice as a means to gauge his illness. His words were telling, but the tone, the candor, the energy of his voice grew more meaningful. Looking back on our almost daily phone conversations, I spent most of my time listening closely to his voice. I would replay our conversations in my head, still unaware that he was going to die, focused on what I could grasp, worried that he felt lonely, that he had a sad day, that he felt far from home, that he felt tired and dizzy from the treatment, all things that I believed that I could improve. I could make him feel close to his friends, I could keep him company over the phone as he lay in the hospital bed, and I could make him feel like a fourteen-year-old. I tried to keep him connected with homework assignments and letters from classmates and videos of our friends. He graciously accepted all of my attempts to save the part of him that I could understand, sustain the part of him that I connected with, to keep him believing in the hope of returning to the lifestyle from which he grew more distanced.

For the most part, I did not realize that behind the tale that he spun for me, that he was facing his death. We even spoke of death on a few occasions, and he convinced me that he was not afraid, once again reassuring me of the very thing that I had quickly dismissed. He made confessions to me about his family's troubles and shared the things that he hoped to do one day. I never saw the connection between his reflections, confessions and worries, but instead believed in his health, his power to recover, the power of medicine, his treatment, the false hope that he would be cured. All the while, I tried to manage the tragic circumstances that he faced in the only way I knew how. In many ways, I never experienced his illness; instead, I experienced the absence of his illness, a space without his illness, which we created together. For the most part, no illness existed over the telephone.

The day that the phone rang and his sister told me that he had died, I was stunned. At that point, after three years of phone conversations and reports on the status of his health, my parents had tried to prepare me for what they recognized as the end of his life. Once again, over the phone, his sister reported to me that he was paralyzed when he died because the cancer had spread to his spine and strangled the spinal cord. His sister shared with me his last secret, something that he actively concealed from me. She told me his secret with the hope that it might be easier for me to deal with his death, knowing how difficult it would have been for the talented soccer player to live paralyzed. As I listened, I felt as if I could not breathe and again, as I write, I feel the same crushing sensation, that he could not tell me his last secret, that he could not break the harmony, that he could not shatter the tale that we spun together even as we spoke the day before his death.

I cannot help but wonder how much he knew about his illness, how much I needed to play into his tale, and how much he wished that he could have told me the truth. Today, I cannot help but wonder how much my new vocabulary of medical school would have revealed to me about his illness, how I would have treated him differently, how I would no longer be able to believe his tale, but now I would have to prepare him for what seemed inevitable.

This time I would be seeing the illness, hearing the illness, watching the illness, understanding the illness, and I would no longer be given the chance to create the tale, to share the tale that he needed to create and I needed to believe. I could no longer participate in the tale spinning; instead, this time, I would have to dismantle the tale, shatter the tale, and stare at the illness directly.

A Private Visit

JONATHAN DWORKIN
MSSM '06

"I'M STARVING," I admitted. A. grinned from under his hat. Then he reached into his coat, a loose beige blazer, and pulled from some secret compartment a tangerine. There was no pause from the driving, his attention remained fixed on the road.

It took some fumbling to peel the fruit, which squirted and resisted until I settled the matter by sinking my teeth in. There were no napkins in the car, so I licked my fingers as best I could. All the while A. drove on, eyes fixed ahead, probing as much for gaps in his own attention as for ice patches or deer crossings. The trip entered its fifth hour, the signs still pointed north.

In a town outside Bangor we passed a complex of smokestacks that bellowed enormous gray plumes into the overcast sky. There were no workers or even cars visible from the road, and the place seemed to run on some kind of autopilot. It felt odd seeing it there in the middle of nowhere, like bumping into an awkward acquaintance on a camping trip, but we passed the stacks and hardly said a word about it.

Sometime later we drove over a bridge. The water below curled like black glass around a mountain, and large chunks of ice perforated its surface and swallowed passing clumps of earth and driftwood. Around us a frozen drizzle made for miserable conditions, but the panorama of the creek winding through the woods snapped us out of our mental spaces. A. stretched his back and gestured towards the radio. This motion possessed a kind of conserved energy, as if his power grew through the exercise of banal tasks. I inserted a cassette and smiled with satisfaction as the fierce piano of Schubert's *Erlkonig* filled the silence of the car. We kept on like that, feeding on the tension of music and forest, until we reached our cabin.

After I gathered my supplies from the car we entered the cabin together. I expected to come across a somber scene, but instead everyone assembled seemed relaxed. Two friends hung over a chessboard while a few others tended to the patient. Someone had taken the trouble to hang white curtains along a broad back window overlooking the woods. The patient rested in bed under some carved bookshelves and a soft reading light. A pale hue clung to him, but when he recognized me he brightened noticeably. Knowing that my work here would be secondary, I took plenty of time to catch up before beginning my exam. He told me of a recent performance in Boston, and though he was too weak to stand, his expressiveness showed that his humor was preserved. He quizzed me on my work, and then on my play. Only after teasing me about the latter did he seem satisfied to undergo the exam.

I continued the light talk through the vitals, and only when I removed his shirt did his decline strike me. He was hollowed out, completely cachectic, and his pallor spread to my face as well. His disease was consuming him from the inside, and no facility invented by man could preserve him any better than our little cabin. I draped him in blankets and called out to A., who helped me reposition him in a chair.

There in the woods, some way north of Bangor, we spent the evening retelling old stories and giving them new twists. There was sadness, but little open grief. A fire burning in a corner hearth provided light and warmth. A. cut some potatoes and stuck them on skewers. This delighted our friend, who insisted on roasting his own. He was all dignity as we began to eat.

Aging

Katherine Krauskopf
MSSM '06

The hour I started to age was fifty years ago.
Normal December 16th, nine days before my birthday,
slush-coated galoshes rested on their rubber mat at the front door
and an orange gauze of winter sun clung above my patch of park
outside the window.
In the bedroom,
I began to change for dinner
before that same crack in the closet mirror
with the same pot of violets on the sill for company.

I began to change for dinner,
pulled dress and slip over my head,
even tossed them onto the edge of the bed.
Turned back to the mirror
to steal a glance at myself before forty became forty-one
and saw the dimple in my skin.
A tiny leaf-shaped dip
moving with each breath,
just above the line cut by my bra across my left breast.
The closer I moved to examine it, hoping for a trick of the fading light,
hoping it would diminish to a figment of the winter day,
the closer I moved, the bigger it became.

The flurry followed—a trip to the doctor, a trip to the specialist, a trip for a second
opinion and then a trip for a third. Of course there was medical treatment—primitive by today's computer screens and machines to image the impossible I imagined on my own.
Time passed. I still pride myself on forgetting its simplest details.
Then two surgeries and less many lymph nodes later, I was deemed in remission.
I was forty-one.
Forty years of before and fifty years of after.
We became comfortable old friends, my remission and I.
Each testing the other's limits
Until enough time passed, and we knew to trust in the silence.
And yet, despite this dependence,
each morning, still smelling of soap and shower,
before I dressed for the day
I would look for another leaf.

I am dying now, although no one knows.
I sit in my white chair, in that same room,
blue and white sheets on that same bed.
Even the violets, which I will give to my daughter, grow.
I sit in my chair across from the closet with its door swung open
so that I am reflected back: white head, round face,
left hand curled and still in my lap—
the more visible scar from surgery,
a small peace of mind
paid for with a bundle of sentinel nodes
and the drowning of my writing hand in pools of edema.

Of course, over time my knees began to creak,
And my spine curved as if obeying laws of tropism for the earth.
Sure my walk slowed and glasses thickened.
And yes these things made me act my age, matched me with my peers at the coffee shop on the corner.

Yet at forty-one—body relatively lithe, strong calves and hair dark and thick,
At forty-one I knew what I would see across the room tonight.
Since then, I have known what to expect from that mirror in the door.

Privacy

Alissa Kahn
MSSM '06

Alonso often sat alone in the shade, staring off into the distance as if contemplating a secret. When I had a rare, quiet moment during the day, with nothing to do and no children climbing on me with mango-sticky hands or clamoring for me to begin a game, I would sit down next to him. He would rest his hand gravely on my arm or his head heavily on my shoulder, but he rarely said a word.

I thought I knew what he was thinking. Unlike most of the other children there, abused or neglected, Alonso was a real orphan. I imagined that while his vivacious seven-year-old sister Graciela was too young to remember their mother and could contentedly spend her days planning her dancing career and avoiding homework, Alonso, at eleven, thought of his mother always, perhaps remembering their poignant last moments together or the texture of her caresses.

That week, I had done my best to avoid the missionaries visiting from Arkansas. When not complimenting me on my "really good English," they were apt to be inviting me to their prayer circle, reminding each other not to drink the (perfectly good) water, or asking me to translate to the children that if they didn't see them again, they would surely see them in heaven. Nonetheless, when on their last day a couple came to me to inquire about adopting Alonso and Graciela, I was pleased.

Earlier that day, another woman had asked me about Lourdes, a dark, dimpled demon who spent much of her time after kindergarten hiding in the bushes trying to catch and kill butterflies. But Lourdes could not be adopted—the state was still fighting her parents in court. So it was with more hope that I translated for this couple as they asked the orphanage director about Alonso and Graciela.

But the answer was no. "Why?" "I don't know," I explained. "She says that they have a disease they inherited from their mother. They're not suitable for adoption." Agitated about the kids, I asked for more information, but that's all she would say. "Maybe some sort of genetic disease?" I weakly offered the missionaries, to which they responded, "Oh, is that why they're so pale?" I tried my best to patiently explain that not all Latin American children have the same exact brown skin color, but I was quite relieved when the missionary group finally left.

I went back to ask again what was wrong with them. Alonso and Graciela were among my favorite children there. But the director was no more forthcoming than before, insisting that she could not tell me any more. I kept repeating my question. Finally, she whispered to me, "Es que tienen el SIDA. Sus padres murieron del SIDA."

So they would never be adopted. Perhaps Graciela would not live to become a dancer—or to not become a dancer. And Alonso would remain alone, carefully considering his secret.

Dean's Lecture

Probing the Onset and Regulation of Erythroid Cell-Specific Gene Expression

JAMES J. BIEKER, PH.D.

Abstract

Cell-restricted transcriptional modulators play a crucial role in the process of selective gene regulation during hematopoiesis. Erythroid Krüppel-like factor (EKLF; KLF1) is a transcription factor, originally identified in this laboratory, which plays a crucial role as a transcriptional activator at the adult ß-globin locus. This review will describe a subset of experiments and approaches related to deciphering its mechanism of action and the means by which it itself is induced.

Key Words: Transcription, EKLF, erythroid cell, gene regulation.

Introduction

UNRAVELING THE MOLECULAR EVENTS that confer the ability to express lineage-specific genes upon an initially uncommitted, pluripotent hematopoietic stem cell remains a major unresolved issue in cell differentiation. This article will describe some of the experiments performed at my lab at the Mount Sinai School of Medicine that address this issue and will show how characterization of a cell-specific transcription factor has opened a window on the processes that lead to erythroid differentiation.

Erythroid Krüppel-like factor (EKLF) was originally isolated by a differential screening approach whereby mRNA that was specifically expressed in erythroid cells was identified after subtraction with common messages expressed in a myeloid cell line (1). Specifically, murine erythroleukemia (MEL) cells provided the erythroid mRNA sample, and the J774 monocyte-macrophage cell line provided the subtracting mRNA sample. This removed 99% of MEL mRNA from consideration. The remaining material was directly cloned. Most of these clones were related to Friend virus genes, metabolic clones (e.g., carbonic anhydrase), and transcription factors (e.g., c-myb and GATA1), but some clones were novel at the time. A Northern blot analysis of adult murine tissues directed the focus to one particular clone uniquely expressed in bone marrow and spleen. Further analysis of this clone (EKLF) indicated that it was expressed only in erythroid cell lines, but not in any lymphoid or myeloid lines, with the exception of a small amount of expression in mast cell lines.

A significant clue as to the function of this clone resulted from the completion of its primary sequence, which indicated that it contained three C2H2-type zinc fingers at the extreme carboxyl end, raising the possibility that it was a DNA-binding protein (1). More precisely, it was most closely homologous to the Krüppel family of transcription factors, which are named after the segmentation gene involved in *Drosophila* body patterning (2). This was fortuitous, as a variety of finger-swapping experiments had been performed with other members of this family (e.g., Zif 268, Sp1, Krox 20) with the aim of predicting its target DNA-binding site. The molecular analysis culminated in the crystallographic structure of Zif 268 bound to its target site (3). Of critical importance for predictive purposes were the interactions of basic residues, at specific amino acid locations, of Zif 268 with guanines within the DNA-binding sequence (4). In addition, each finger interacted with a triplet of nucleotides. This information enabled us to predict that EKLF would interact with 3'GGNGNGGGN5'.

Address all correspondence to James J. Bieker, Ph.D., Box 1020, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

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Glossary

BAF = BRG associated factors
BMP = bone morphogenetic protein
BMPR = BMP receptor
CBF = copper-binding protein
CFU-E = colony-forming unit-erythroid
DN = dominant negative
EB = embryoid bodies
E-RCI = EKLF remodeling complex-1
ES = embryonic stem
EKLF = Erythroid Krüppel-like factor
HS = hypersensitive site
LCR = locus control region
MEL = murine erythroleukemia
P/CAF = p300/CBP associated factor
SUMO = Small Ubiquitin-like Modifier

A subset of this sequence, known as the 5'CACCC3' element, was already recognized as one of a trio of elements that are repeated within erythroid enhancers and promoters. In particular, the CAC site within the ß-globin gene (5'CCACACCCT3') precisely matched the predicted EKLF consensus binding sequence. An oligonucleotide containing this sequence was directly tested and found to bind EKLF *in vitro* with high affinity. In addition, transfection studies demonstrated that EKLF functioned as a transcriptional activator (not repressor) when bound to this site. These studies provided the initial isolation and characterization of this transcription factor (1).

Functional Role of EKLF in Erythroid Expression

The ß-globin gene CACCC element is the site of thalassemia-causing point mutations in humans (5). Given this fact, individual examples of these elements were directly tested for their ability to interact with EKLF (6). The results were dramatic: Not only was EKLF unable to transactivate through these mutated sites, but also the binding affinity was decreased 40- to 100-fold. Molecular modeling of these interactions indicated that both specific and non-specific hydrogen bond interactions were adversely affected by what appeared to be minor changes in the sequence of the CACCC element. Methylation interference assays further demonstrated that each of the guanines on the G-rich strand in the nine-base-pair ß-globin CACCC element (3'**GGTGTGGG**A5') were critical for optimal binding by EKLF.

To understand the potential importance of these properties, a brief summary of ß-globin regulation is needed. Expression of the ß-like globin genes is regulated in a specific temporal sequence during mammalian development (5, 7, 8). In humans, the first blood cells formed within the yolk sac express the embryonic (epsilon) globin variant. After the site of hematopoiesis switches to the fetal liver, the fetal (gamma) globin genes are expressed. This is followed by yet another switch in expression to the adult (ß) globin gene after the bone marrow becomes the major site of hematopoiesis. In mice, there is a single switch in molecular expression from embryonic (y, bh0, bh1) globin genes in the yolk sac to the adult (ß) globin variant in the fetal liver and the adult bone marrow and spleen. Regulation of this large ß-like globin cluster is thought to occur by competition of each globin promoter member (embryonic, fetal, and adult) for interaction with the locus control region (LCR), thus enabling high-level activity of only one member at its appropriate time during development. In reality, this control is more complex, as an endogenous silencing mechanism also plays a vital role in this process (7 – 10).

Hints that EKLF's role in ß-globin regulation is complex followed from the point mutation analysis described above. Specifically, the murine embryonic (and human fetal) CACCC elements differ in one of the important guanines within the interaction sequence, 3'G**A**GGTGGGT5' (11). Given the deleterious effects of the thalassemia-causing point mutations, it was felt that this change would also adversely affect binding. This hypothesis was directly tested, and competition assays demonstrated that the embryonic CACCC element had an 8-fold lower affinity for EKLF compared to the adult CACCC element (12). The effects of such a mutation were tested *in vivo* by using K562 cells, a human erythroleukemic cell line that expresses gamma, but not ß, globin. In this line, EKLF had minimal effects on the activity of an intact gamma globin promoter, but could specifically activate the ß-globin promoter more than 1000-fold when it was linked in cis to the gamma promoter. These molecular data raised the possibility that EKLF may be important for the switch from fetal to adult ß-like globin expression and led to the prediction that an EKLF-null mutation would lead to deficiency in adult, but not in embryonic or fetal, globin expression, a conjecture that was borne out by its genetic knock-out in mice (13, 14). This led to an embryonic-lethal phenotype by day 14, due to lack of onset of ß-globin transcription, resulting in extreme anemia and prenatal death, precisely at the time of the switch; embryonic globins were expressed at normal levels. These effects were unusually specific, since alpha-globins and other red-cell-specific genes were unaffected by the lack of EKLF expression. Additional studies that utilized EKLF-null embryonic stem cells to generate chimeric adult mice indicated that these cells did not contribute to the mature erythrocyte population, and that they were defective by virtue of a globin chain imbalance, leading to Heinz body formation, a shortened lifespan, and apparent clearance from the bloodstream (15).

These data revealed that EKLF is critical for the onset of adult ß-globin expression. To address the effects on the other linked globin-like genes in the cluster, EKLF-null mice were crossed with a murine line that carries the complete human ß-like globin cluster (16, 17). As seen with the murine locus, adult ß-globin expression was completely dependent on EKLF. However, gamma-globin levels were 5-fold higher, and although they were eventually silenced (as the mice still died from lack of adult ß-globin expression), this shut-off occurred significantly later than that observed in the presence of EKLF. In addition, most EKLF-null, colony forming unit-erythroid (CFU-E) colonies were reprogrammed to high gamma-globin expression. The mode of EKLF action thus appears to involve consolidating the switch from fetal to adult globin, possibly by enabling the ß-globin promoter to form a structure that is able to compete for interaction with the LCR to a greater extent than the embryonic- or fetal-globin promoters.

Mechanism of EKLF Transcriptional Activation

Two aspects of EKLF function were studied. One was the possible role that post-translational modification plays in EKLF activity, since the minimal activation and inhibitory domains each contain conserved sites for serine/threonine phosphorylation (18). In fact, one of the double-amino acid mutations (at aa 43–44) that disrupted the *in vivo* competitive ability of EKLF overlapped with a casein kinase II site (threonine at aa 41). As expected, immunoprecipitation of EKLF from erythroid cells revealed that EKLF is a phosphoprotein *in vivo*, exclusively at serine and threonine (no evidence was seen for modification of tyrosine). In addition, EKLF is a suitable substrate for casein kinase II *in vitro*. Further, the double mutant, or a direct mutant of thr41, was not able to transactivate a reporter *in vivo*. This loss was not observed when the charge at aa 41 was retained (i.e., after conversion to aspartic acid). The location of this important phosphorylation site within the interaction domain of the minimal activation region raises the possibility that EKLF interactions and activity may be modulated by phosphorylation.

The second aspect of EKLF function that was considered in the deletional studies was the importance of protein-protein interactions. The possibility that EKLF may also be involved in chromatin structure at the ß-globin locus led to directly testing whether it interacted with the class of molecules known as histone acetyltransferases (19). These are known to modify histones via acetylation of the amino terminal tails, leading to a more open chromatin structure at that region, thus enabling the transcription machinery to be fully recruited and active (20, 21). The finding that some transcriptional co-activators (such as CBP, p300, and P/CAF) harbor intrinsic histone acetyltransferase activity suggests a mechanism to directly link transcriptional activation and alteration of chromatin structure (22). In the present case (19), EKLF was found to associate with p300, CREB-binding protein (CBP), and p300/CBP associated factor (P/CAF) *in vivo*. Interestingly, EKLF is itself acetylated by p300 and CBP *in vitro*, but not by P/CAF. These sites have been mapped to two lysines (288 and 302). Mutation of lys-288 (but not lys-302) decreases EKLF transactivation of the ß-globin promoter and disables its ability to be superactivated by p300 and CBP (23). EKLF interactions with proteins, rather than with DNA, are affected by its acetylation. In addition to these post-translational modifications (Fig. 1), EKLF is also SUMOylated (SUMO: Small Ubiquitin-like Modifier) (Siatecka and Bieker, unpublished) and ubiquitinated (Quadrini and Bieker, unpublished).

An additional area in which EKLF-protein interactions may be playing an important role is in chromatin remodeling (24, 25). Using an *in vitro* chromatin reconstitution/transcription system, EKLF and a MEL-derived cell extract (EKLF remodeling complex-1; E-RC1) were both

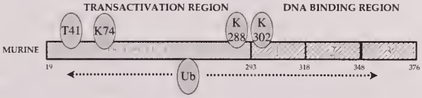


Fig 1. Post-translational modification of EKLF protein. A schematic diagram of EKLF shows its transactivation (amino terminal) and DNA binding (carboxyl terminal) regions. The DNA binding region contains three C2H2 zinc fingers. Also indicated are the locations of important phosphorylation (T41), sumoylation (K74), acetylation (K288 and K302), and ubiquitination (throughout) sites discussed in the text.

required to provide an open chromatin structure and transcription at the ß-globin promoter (26). In the absence of either component, or by using a mutated EKLF binding site, the chromatin structure remained closed and refractory to transcription. Use of an EKLF deletion that had removed its amino terminal interaction domain still bound DNA and yielded an open chromatin structure, but no transcription was observed, thus uncoupling the two events. Intriguingly, purification of E-RC1 helped identify mammalian components of the SWI-SNF chromatin remodeling proteins, including BRG1, BAF (BRG1 associated factor) 170, BAF155, BAF47, and BAF57. Immunoprecipitation or immunoneutralization of this complex from the MEL fraction again led to an inability to activate the promoter. Interaction of EKLF with BRG1 appears critical for interaction with SWI-SNF (27).

These studies, taken together, implicate EKLF as a central player in the integration of a variety of signals that lead to protein modification, protein-protein interactions, opening of chromatin, and activation of transcription. There is ample precedent for each of the steps in this pathway from other systems, and a testable challenge for future studies will be to determine just how EKLF functions. The biological relevance of these studies has followed from studies that crossed the EKLF-null mice with mice that are transgenic for the complete human ß-like globin locus (17). These studies demonstrated that the hypersensitive site (HS) at the ß-globin promoter is absent when EKLF is not present. In addition, HS3 within the LCR was adversely affected. Thus, not only is EKLF required for transcription of ß-globin *in vivo*, but it also plays a role in forming the correct higher-order structure at the globin locus (28). EKLF interactions with histone acetyltransferases and with chromatin remodeling proteins provide a mechanism that partially accounts for how this may occur.

Regulation of EKLF Expression

Analysis of EKLF biological expression has also provided critical information about its role (29). EKLF is not expressed in embryonic stem (ES) cells, but becomes apparent during embryoid body differentiation in culture. Analysis of developing murine embryos indicated that EKLF is first expressed at the neural plate stage (i.e., day 7.5) within the extraembryonic mesoderm of the visceral yolk sac, the earliest morphologically identifiable time of blood island formation, after which its level continues to expand. It is then expressed at day 9.0 within the hepatic primordia, and by day 14.5 the fetal liver is the only site of EKLF expression. In the adult mouse spleen, it is expressed solely within the red pulp.

Because of these erythroid cell-specific properties, EKLF's own regulation has been investigated (30–32). Both the murine and human genomic clones have been isolated, sequenced, and mapped (33, 34). A surprisingly short region of the promoter is sufficient to reconstitute erythroid specificity to an adjacent reporter (30). Although there is no TATA sequence, the proximal promoter region contains GATA and CCAAT sites. The importance of these sites was verified by transfection assays in erythroid cells (MEL and 32DEpo1 lines). More distal elements have been implicated by identifying erythroid-specific DNAse hypersensitive sites at the EKLF genomic locus (31). Two sites within 1000 bp 5' of the transcription start site were identified by this approach. The sequence surrounding the more distal hypersensitive site not only is highly conserved with the human EKLF promoter (Lohmann and Bieker, unpublished), but also behaves as a strong enhancer element, even when placed adjacent to a non-erythroid promoter. However, erythroid specificity can be reestablished when this element is placed adjacent to the EKLF promoter, with the proximal GATA site proving critical for this enhancement (31). Experiments with transgenic mice that contain a ß-galactosidase reporter whose expression is directed by EKLF promoter elements reveal that this short piece is sufficient to generate expression in the blood islands as well as in the fetal liver (35). In addition, both hypersensitive sites, along with the proximal promoter, are all required for this effect. Experiments with 32DEpo1 cells have directed attention to a 49 bp sequence within the most conserved, distal hypersensitive site, which contains the core sequence responsible for enhancement and contains three protein-binding sites *in vitro* (31).

Conditions to differentiate embryonic stem cells to embryoid bodies (EBs) in the absence of serum were established in order to identify cytokines responsible for induction of EKLF expression during early development (36). These studies, in conjunction with expression of dominant negative proteins, enabled us to conclude that the BMP (bone morphogenetic protein) 4/BMP receptor/Smad pathway plays a critical role in EKLF induction (Fig. 2).

Additional Unresolved Issues and Future Directions

A paradox follows from the observation that EKLF message is expressed in both primitive (yolk sac) and definitive (mouse fetal liver) erythroid cells, yet is functionally only required for definitive erythropoiesis. Since EKLF protein is present in both populations, it has been proposed

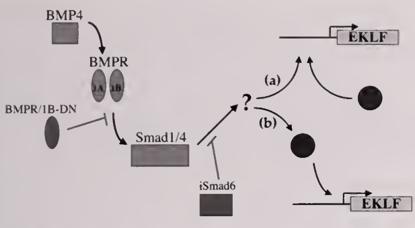


Fig. 2. Models of EKLF induction by BMP4.
Our induction (BMP (bone morphogenetic protein) 4/BMPR (BMP Receptor)/Smad1/4 (dimer of Smad1 and Smad4 proteins)) and stable inhibitor (BMPR/1B-DN (dominant negative BMP Receptor 1B) and iSmad6 (inhibitory Smad6)) studies (36) implicate the BMP pathway as indicated. The delayed nature of this effect leads to postulating a required novel protein (circle) that is synthesized independently (a) or dependent (b) on the Smad complex. At the same time, the Smad1/4 complex itself may still play a role in EKLF induction in conjunction with its own target novel protein (not shown).

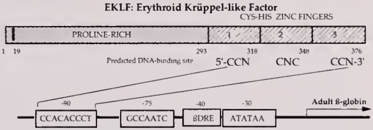
that post-translational modification or changes in protein-protein interactions might yield functionally altered EKLF states at different stages in development. This conundrum extends even deeper, as EKLF message is detected quite early in hematopoietic differentiation, since it is already transcribed both in multipotential cell lines (37, 38) and in enriched primary progenitors (early differentiating CD34+LIN- cells [39]). Again, the reason why EKLF should be expressed so precociously when its requirement is considerably later in differentiation, and whether this is functionally important, remains to be resolved.

Another issue of intense interest is whether there are any other downstream targets of EKLF besides ß-globin. This issue arises primarily because a large number of erythroid gene promoters contain CACCC elements that theoretically should interact with EKLF.

The importance of both the DNA binding and transactivation modules of EKLF in regulating ß-globin transcription and chromatin structure has inspired approaches to take advantage of these structures, to alter globin regulation. For example, modifying the EKLF fingers to bind the defective CAC site, thus providing a therapeutic agent that increases levels of delta-globin expression in ß-thalassemic or sickle cell patients. Alternatively, changing the EKLF activation module to a transrepressor could alter the structure of the locus enough to silence ß- yet reactivate the gamma-globin gene, thus achieving the same end (Manwani and Bieker, unpublished).

Summary

EKLF clearly plays a crucial role in the controlled events that lead to developmental regulation of the ß-like globin cluster (Fig. 3). As a result, structural and functional analysis of EKLF has enabled us to open a molecular window on the process of ß-globin gene regulation. Each EKLF module plays an important part in its functional specificity. The zinc fingers discriminate among very similar CACCC elements, and the transactivation domain plays a critical role in transcriptional activation and in opening the surrounding chromatin. Protein-protein interactions are pivotal for this process; in this context, it will be critical to determine whether post-translational modification (phosphorylation, acetylation, sumoylation, and ubiquitination) of EKLF is regulated during hematopoiesis and/or during development, and how this affects the efficiency of these interactions, and thus of the onset of ß-globin expression. Any tie-in of these changes to the action of extracellular effectors will be critical for understanding the complete transduction cascade involved in the onset of ß-like globin transcription during development.



Expression : -bone marrow and spleen
-limited to erythroid and (low level) mast cell lines
-in both primitive and definitive erythroid cells
Structure/Activity : -contains a potent transactivation module specifically required for adult ß-globin expression in the erythroid cell
-transactivation module is phosphorylated and multifunctional
-zinc fingers form close contacts to G-rich strand
-will not bind to nor transactivate from ß-thalassemia mutant CACCC elements
-preferentially binds and activates the adult ß-globin CAC site over embryonic and fetal CAC sites
-interacts with and becomes acetylated by histone acetyltransferases
-required with remodeling proteins for chromatin reconstitution/ transcription at the ß-promoter
Biological Function : -genetic disruption causes severe ß-thalassemia and embryonic death at the time of switch to ß-globin expression in mice
-facilitates the silencing of fetal globin expression; crucial factor for γ-ß switching
-critical for proper chromatin structure at ß-promoter and at the LCR

Fig. 3. Summation of EKLF structure/function.
Diagram of EKLF, demarcation of its zinc fingers and their relation to its predicted binding site, and location of its actual ß-globin CACCC element binding site. The numbers below the protein scheme denote amino acids, while those above the ß-globin gene denote the base position upstream to the transcriptional start. A recapitulation of EKLF's role in erythroid gene control as discussed in the text is outlined.

Acknowledgments

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Iloprost in Embolic Renal Failure

Tal Grenader, M.D.[1], Meyer Lifschitz, M.D.[2], and Linda Shavit, M.D.[2]

Abstract

Cholesterol embolism is a serious disease with a high morbidity and mortality rate. There is no clear evidence that any specific treatment helps this syndrome. We report a patient who developed acute renal failure due to cholesterol crystal embolism following percutaneous transluminal angioplasty of a renal artery. Treatment with iloprost for peripheral symptoms of cholesterol emboli resulted in rapid resolution of toe cyanosis, decrease in leg pain and a significant decrease in serum creatinine shortly after initiation of treatment. One month after initiation of iloprost therapy, skin signs of cholesterol emboli disappeared and leg pain diminished. Gradually reduction in serum creatinine level was also observed (from 390 to 160 micromol/L). Eighteen months after the arteriography, the patient had stable renal function with creatinine levels of 150 – 160 micromol/L, and he was asymptomatic.

Key Words: Cholesterol crystal emboli, iloprost, acute renal failure.

Introduction

Cholesterol crystal embolism is a multisystem disorder characterized by the occlusion of small arteries by cholesterol crystal particles which originate in ruptured atherosclerotic plaques in the aorta or, occasionally, in other large arteries (1, 2). Atheroembolism may occur spontaneously or it may occur secondary to endovascular trauma such as vascular surgery or angiographic procedures. Other etiologic factors include anticoagulation and thrombolysis. A number of patients may experience multiple triggering factors (1, 2). The proximity of the kidney to the abdominal aorta and the rich renal blood supply make the kidney a frequent target organ for atheroemboli.

Cholesterol embolism is a serious disease with a high morbidity and mortality rate. There is no clear evidence that any specific treatment helps this syndrome. We report a patient with multiple cholesterol crystal emboli in the kidneys and in the lower extremities, who had significant improvement in limb ischemia and renal function after intravenous iloprost therapy.

Case Presentation

A 52-year-old male complaining of severe headache was admitted for investigation. The patient had been suffering from hypertension for six years and was being treated with controlled-release nifedipine. He had a history of hyperlipidemia, heavy smoking and two cerebrovascular accidents, two and five years earlier. Two weeks before the current admission, the patient had complained of severe headache and was examined by the family physician. Enalapril was added to his treatment because of uncontrolled hypertension (200/100 mm Hg). On admission the patient was slightly irritable and agitated. His pulse rate was 75 beats per minute and his blood pressure was 220/110 mm Hg. He was afebrile. Fundoscopic examination revealed arteriovenous nicking and multiple, flame-shaped hemorrhages, but no papilledema. The lungs were clear. Heart sounds were regular, without murmurs. The abdomen was soft and non-tender. There was no edema of the lower extremities. The pulses were palpated on all peripheral arteries. Loud murmurs were heard over both femoral arteries and over the right renal artery. Neurological examination showed pyramidal signs consistent with an old left hemispheric stroke. The electrocardiogram showed normal sinus rhythm and voltage criteria for left ventricular hypertrophy.

The laboratory test results showed mildly impaired renal function (creatinine 110 micromol/L,

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From the [1]Department of Medicine, Hadassah University Hospital, and [2]Department of Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel.

Address all correspondence to Tal Grenader, M.D., Department of Medicine, Hadassah University Hospital, P.O. Box 12000, 91120 Jerusalem, Israel; e-mail: talgrenader65@hotmail.com

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urea 6.9 mmol/L), mild anemia (hemoglobin 11.3 mg%) and elevated blood cholesterol level (5.4 mmol/L). Potassium level was 4 mmol/L. Other laboratory tests were unremarkable.

Intravenous nitroglycerin worsened the headache without lowering the blood pressure. Intravenous hydralazine resulted in a prompt normalization of blood pressure.

Renal ultrasound demonstrated right and left kidney long axes measuring 11.5 and 10 cm, respectively. A renal technetium-DTPA flow scan showed significant reduction of perfusion of the left kidney (less than 5% normal). Uptake, concentration and excretion of isotope from the right kidney were normal. The patient underwent renal angiography, which demonstrated severe narrowing of the right renal artery. The left renal artery was totally occluded and no filling of the left kidney could be demonsrated. An initial attempt of stent insertion to the right kidney failed. Three days later a second renal angiography, under general anesthesia, was performed with successful stent insertion into the right renal artery. Angioplasty of the left renal artery was considered futile.

During the next two days the patient reported feeling well, and his kidney function was stable. On day three he started to complain of severe leg pain, and physical examination revealed livedo reticularis of both lower extremities, flank and buttocks, and scattered purple discoloration of feet and toes. The fundoscopic examination revealed no evidence of cholesterol emboli. Laboratory blood tests showed a significant deterioration of renal function with a rise in serum creatinine (220 micromol/L), and urea (6.8 mmol/L), eosinophilia (total eosinophil count 1,500 per mm^3), elevated creatinine phosphokinase (1,100 units: normal 0 – 170 units) and myoglobin (224 ng/mL: normal 0 – 70 ng/mL). The blood homocysteine level was significantly elevated (29 nmol/mL: normal 0 – 15 nmol/mL). Screening tests for hypercoagulable state, including antiphospholipid antibodies, antithrombin III, lupus anticoagulant, activated protein C resistance and protein C and S, were within normal limits. A second renal ultrasound with Doppler showed normal blood flow to the right kidney, with no evidence of stent occlusion. Peripheral artery Doppler examination showed no hemodynamically significant arterial disease of the lower limbs, including the toes. Skin biopsy from one of the ischemic toe lesions showed cholesterol clefts. Atheroembolic renal disease due to embolization of cholesterol particles to the lower extremities and kidneys was diagnosed. During the following days, the patient remained clinically and biochemically stable. His blood pressure was 160/90 mm Hg with hydralazine, felodipine and atenolol therapy, and he was then discharged.

Two weeks later, the patient was readmitted with worsening leg pain and further deterioration of renal function. His plasma creatinine level was 390 micromol/L. Blood pressure was stable. Doppler ultrasound showed patent flow in the right renal artery. There was no improvement with intravenous fluids.

Adequate analgesic therapy with oxicontin was given. Two weeks of observation showed no improvement of renal function or lower extremity pain. The patient continued to have severe pain in his lower limbs. Based on a report of clinical improvement of cholesterol emboli with iloprost, a twenty-day course of intravenous iloprost (prostacyclin analogue) 25 mcg/daily was initiated (3). The treatment was then continued with 25 mcg iloprost once weekly for one year. One month after initiation of iloprost therapy, skin signs of cholesterol emboli (livedo reticularis and discoloration of the toes) disappeared and leg pain diminished. Gradually, reduction in creatinine level was also observed (from 390 to 160 micromol/L). Eighteen months after the arteriography, the patient had stable renal function with creatinine levels of 150 – 160 micromol/L and was asymptomatic.

Discussion

Our patient had developed acute renal failure due to cholesterol crystal embolism following percutaneous transluminal angioplasty of a renal artery. Multiple risk factors for atherosclerosis, such as male sex, hypertension, cigarette smoking, elevated homocysteine level and hyperlipidemia were present in our patient. These factors increase the risk for embolic as well as thrombotic disease.

In our patient, the classical triad of a triggering event, acute renal failure and peripheral crystal embolization (suggested by livedo reticularis and patchy purple discoloration of lower limbs associated with severe pain and cholesterol cleft on skin biopsy) supported the diagnosis of cholesterol crystal embolism syndrome. Laboratory test results also supported the diagnosis. Eosinophilia appears to be the most common extrarenal laboratory feature of cholesterol crystal embolism. Elevated creatinine phosphokinase and myoglobin levels suggested myositis secondary to emboli in our patient.

At present, there is no known treatment for the serious condition of atheromatous emboli. Thus, any therapeutic approach that might be of benefit deserves consideration. Steroid treatment is controversial. Recent reports suggest that steroid therapy might be useful for specific patients (4). In previous studies, however, the use of corticosteroids was associated with high mortality (2).

Treatment is mostly supportive. This includes proper control of hypertension and heart failure, adequate nutrition and hydration, and support of renal function with dialysis if necessary. Surgical treatment (removal of diseased vessel wall) may be curative, but is associated with a prohibitively high mortality rate.

It is interesting to consider the possible mechanism(s) for acute renal failure in this patient. Surely the clinical presentation, including previous strokes and decreased kidney function on the left side, suggests pre-existing atherosclerotic disease. The acute changes after renal angiography are diagnostic of peripheral atheroembolic disease, and when acute renal failure occurs in this setting, it is strongly suggestive of atheroembolic renal disease. Could this be contrast-induced nephropathy? Contrast-induced nephropathy almost always occurs during the first 24–48 hours after angiography and resolves within the next few days. This patient had stable kidney function during the two first days following contrast exposure. His renal injury gradually progressed over two weeks until iloprost was started. Thus, this clinical sequence is much more consistent with atheroembolic kidney disease than with contrast-induced nephropathy.

Treatment with iloprost for peripheral symptoms of cholesterol emboli in our patient resulted in rapid resolution of toe cyanosis, improvement of leg pain and a significant decrease in serum creatinine level shortly after initiation of treatment. Iloprost, a stable prostacyclin analog with strong vasodilating and platelet antiaggregating effects, has been shown to be highly effective in treating many diseases, including peripheral vascular disease, pulmonary hypertension and Raynaud's phenomenon (5).

The effects of iloprost on renal plasma flow, renal function and the renin-angiotensin system have been studied in patients with peripheral vascular disease and normal renal function (6). This study demonstrated significantly increased renal plasma flow and fractional excretion of sodium without affecting glomerular filtration rate or plasma renin activity. Prostaglandin I2 and its stable analog iloprost have been shown to protect the kidney in several models of experimental renal injury (7, 8).

In a series of 10 patients with systemic sclerosis and elevated resistance index of renal vessels, iloprost administration reduced the resistance index after both acute and chronic drug administraton (9). A recent report describes four cases of cholesterol emboli treated with iloprost. The main observations were improvement in distal extremity ischemia in all cases and improvement in renal function in the one patient with acute renal impairment (3). In a patient with renal artery embolism, iloprost led to improvement in renal function recovery (10).

The benefits of iloprost in pulmonary hypertension and chronic pulmonary thromboembolism, as well as in some studies of acute renal failure, certainly warrant further exploration in animals and man.

It is generally accepted that prostaglandins act as local regulators of vascular tone. They directly vasodilate afferent and efferent arterioles. In addition, prostacyclin inhibits the production of endothelin, a potent vasoconstrictor peptide. This property of iloprost may explain its effectiveness in patients with renal impairment due to renal vasospasm. However, the mechanism of action of iloprost in this patient with cholesterol embolism is unclear and needs to be investigated.

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Open Preperitoneal Mesh Repair of Recurrent Inguinal and Femoral Hernias

George H. Sakorafas, M.D., Christos Nissiotakis, M.D., Ioannis Chalikias, M.D.,
Nikolaos Kotsifopoulos, M.D., Alexios Stavrou, M.D., and George A. Kassaras, M.D.

Abstract

Recurrences of inguinal hernias are a not infrequent problem seen by the surgeon. Usually, repair of these hernias is technically more demanding than the original repairs, with potential for a new recurrence, and a higher risk of complications. Open preperitoneal placement of prosthetic mesh is an effective method of repair for such recurrences. It can easily be performed, using epidural or caudal anesthesia, in the intact preperitoneal space, with extremely low recurrence rates, low morbidity, and high patient satisfaction. We present our experience with this technique in 27 patients during a 7-year period. Mean follow-up was 45 months. The procedure was safe (no significant early and late morbidity) and achieved a safe repair (no recurrence during the follow-up period).

Key Words: Inguinal hernia, recurrence, mesh, tension-free repair, recurrent inguinal hernia.

Introduction

About a century ago, Bassini established the era of modern anatomic hernia surgery (1). Yet despite subsequent advances and refinements of surgical techniques and materials used, recurrences have remained a significant problem. In an attempt to reinforce the repairs and prevent recurrences, surgeons have used many autologous tissue techniques, and homologous and heterologous tissue biomaterials (2). Polyethylene was first proposed by Usher in 1959, to repair tissue defects of the chest and abdominal wall (3). Since that time, there has been intense interest in the use of polypropylene and other synthetics for plastic hernia repair. This interest grew during the last decade of the 20th century, probably as a result of the reports by Stoppa et al. (4, 5), as well as the innovation of laparoscopic hernia repair, in which mesh is routinely used (6, 7). The preperitoneal approach, using a prosthetic mesh, is an attractive method for repairing recurrent inguinal hernias, since it offers many theoretical advantages, such as strength, tension-free repair, optimal surface area for tissue incorporation, and positioning of the mesh in the intact preperitoneal space. In this article, we review our experience with this method in 27 patients.

Patients and Methods

From June 1995 through February 2002, 27 patients (26 males and 1 female) underwent tension-free repair of recurrent inguinal hernias (26 males) and a recurrent femoral hernia (the female patient) with the polypropylene mesh (Surgi-Pro®), using the open preperitoneal approach. Median patient age was 65 years (range: 45 – 78 years). All the male patients had had their inguinal hernias originally repaired by the Bassini technique, while the female patient had had a femoral hernia repair using the below-the-inguinal-ligament approach. One patient had had bilateral inguinal hernias. In another patient, the inguinal hernia had recurred twice. All patients had their original surgery under epidural anesthesia.

Surgical Technique

The procedure is performed with patient under epidural or caudal anesthesia. A Foley catheter is

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From the Department of Surgery, 251 Hellenic Air Force Hospital, Athens, Greece.

Address all correspondence to George H. Sakorafas, M.D., Ph.D., Arkadias 19 – 21, GR - 115 26 Athens, Greece; e-mail: georgesakorafas@yahoo.com

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inserted just before the operation, especially in elderly patients. The incision is made slightly above the incision used in the conventional anterior (inguinal canal) repair. It begins just lateral to the midline, approximately 2 cm above the pubic tubercle, and is directed to a point about 1 cm superior to the projected location of the deep inguinal ring. The incision must be made so that it is slightly above both the deep inguinal ring and the hernia defect. The anterior rectus sheath is transversely incised. This incision is carried laterally, incising the aponeurosis of the external oblique, separating the internal oblique and the transversus muscles in the line of their fibers, and opening the transversalis fascia. The underlying peritoneum is not opened. The inferior epigastric vessels are ligated, since this allows a wide exposure of the preperitoneal space and greatly facilitates appropriate mesh placement. By retracting the pelvic peritoneum and preperitoneal fat away from the posterior inguinal wall, the hernia is easily recognized and reduced after the identification of the vas deferens and the spermatic blood vessels. The hernia defect is left unsutured. The femoral vessels are easily identified. A small opening is made on the mesh to accommodate the spermatic cord and vessels (Fig. 1). The next step is the placement of the mesh. Prolene® sutures (no. 2-0 or 3-0) are placed in the pubic tubercle, in the Cooper's ligament, and then along the iliopubic tract to the iliopectineal arch, and left untied. These sutures are then passed at the lower border of the mesh, left untied, and held in hemostats. The mesh is then anchored in place by tying the sutures (Figs. 2 and 3). The external oblique aponeurosis is elevated in the superior part of the incision, thus exposing the internal oblique muscle. The medial, superior, and lateral borders of the mesh are then anchored in the musculofascial abdominal wall by mattress sutures of 2-0 Prolene, which are placed through the full thickness of the musculofascial wall, the prosthesis, and then again through the muscular abdominal wall (Figs. 3a and 3b). A "bite" of about 1 cm of tissue is included in these mattress sutures. A closed suction drain is placed on the surface of the prosthesis and is then extracted through a stab wound.

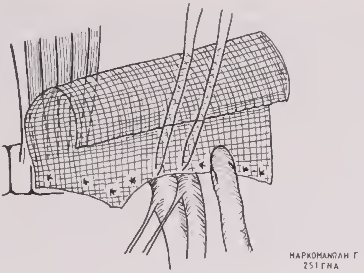


Fig. 2. Prolene sutures are placed in the pubic tuburcle, in the Cooper's ligament, and then along the iliopubic tract to the iliopectineal arch and left untied.

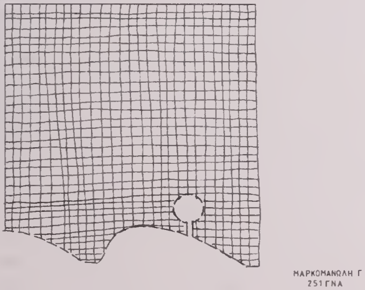
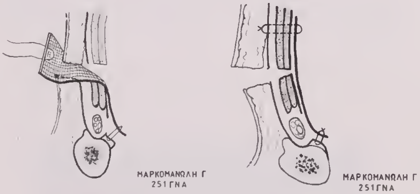


Fig. 1. A small opening is made on the mesh to accommodate the spermatic cord and vessels.

Results

The hospital stay for the procedure was 1–3 days (mean: 1.4 days). None of our patients experienced significant early morbidity postoperatively. In the patient with bilateral hernia repair, a macroscopic hematuria was observed on the day of surgery; it resolved spontaneously and was attributed to the maneuvers (pressure) on the urinary bladder during surgery. All patients were mobile by the evening of the day of surgery. The Foley catheter was removed immediately after surgery or on postoperative day 1. Pain was minimal in all patients and was easily controlled by the use of sim-



Figs. 3a and 3b. The mesh is anchored by suturing the previously placed sutures.

ple, non-opioid analgesics (paracetamol). The drain was removed just before the patient was discharged. Patients returned to their usual activities approximately ten days following surgery. They were instructed to avoid lifting excessive weight (> 10 kg) for at least one month. Follow-up for 22 of the patients was completed by clinical examination. Mean follow-up period was 45 months (range: 1 – 74 months) (Fig. 4). There was no hernia recurrence during this period. None of the patients examined at follow-up experienced late morbidity (such as neuralgia).

Discussion

Stoppa in France described the concept of preperitoneal, tension-free placement of prosthetic mesh in the surgical repair of inguinal hernia in the 1970s (4). Since that time, the use of prosthetic materials has increased rapidly. There is evidence that in adult patients with inguinal hernia, a metabolic defect in collagen synthesis is involved. Therefore, the wound requires the tensile strength of the mesh to achieve a strong repair. This is especially important in recurrent hernias. Unfortunately, the ideal mesh prosthetic is yet to be found. Existing data suggest that absorbable mesh does not remain in the wound long enough for adequate collagen to be deposited (8). Multi-filament mesh can harbor bacteria in spaces too small for normal body mechanisms to eliminate them. Mesh that fibroblasts cannot adhere to and infiltrate does not lead to the desired strengthening of the inguinal wall. Monofilament mesh is the most popular presently in use, with the various types of polypropylene having different characteristic advantages (8 – 10).

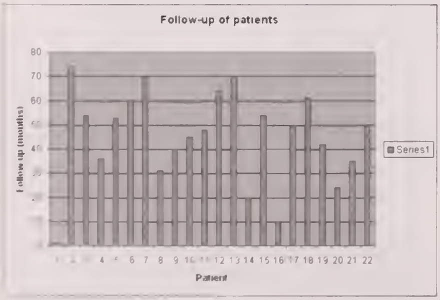


Fig. 4. Follow-up for each of the 22 patients. Although late recurrences are seen, most take place within the first 2 years following repair As illustrated in this diagram, the follow-up was > 24 months for 19 patients

Despite the problem of not yet having the ideal material, the method itself offers many theoretical advantages (4, 5, 11):

1. By preserving the hernia sac, a layer of viable autogenous tissue persists to serve as a barrier between the prosthesis patching the defect and the intraperitoneal contents, thereby minimizing the incidence of fistula or bowel obstruction.
2. Intraparietal placement of the prosthesis allows well-vascularized, soft tissue coverage of all aspects of the prosthesis.
3. Use of porous mesh (polypropylene) allows a large surface area for in-growth of connective tissue, leading to permanent fixation of the prosthesis within the abdominal wall.
4. With the preperitoneal placement of the mesh, intra-abdominal pressure tends to hold the mesh in place against the posterior surface of the anterior abdominal wall (in contrast to the on-lay technique).
5. This technique is a tension-free method that patches the defect rather than attempting to close it by re-approximating fascia edges under tension.
6. Finally, from a technical point of view, the preperitoneal space is typically intact during repair of recurrent hernias, and this greatly facilitates the procedure.

The patients are easily mobilized not long after the surgery, generally on the same day. Postoperative pain is minimal, mainly due to the absence of tension in this type of hernia repair. And the procedure is associated with minimal morbidity. Possible complications include seroma, hematoma, infection, and neuroma. The first two can be prevented by meticulous hemostasis and by the placement of a closed suction drain at surgery. Other potential complications, such as injury to the bowel or bladder, can usually be avoided by careful dissection during repair.

Endoscopic repair of recurrent inguinal hernia is another alternative technique, which also achieves satisfactory results (12, 13). However, this approach requires significant experience in laparoscopic surgery. General anesthesia is also required, and this may be a problem, especially for patients with significant co-morbidity.

In the era of tension-free inguinal hernia repair using prosthetic meshes, recurrences are much less common than in the past. In our department, the Lichtenstein technique is the preferred method for inguinal hernia repair (14, 15). However, when facing a patient with a recurrent inguinal hernia, the surgeon should bear in mind that preperitoneal, open, tension-free repair using a polypropylene mesh is a simple and effective method, with extremely low recurrence rates, low early and late morbidity, and high patient satisfaction. The preperitoneal space is typically unaltered, and this is the main advantage of this approach. The recently proposed "mesh and plug" technique is a relatively easy, safe, and effective alternative method for the management of recurrent inguinal hernias, using the tension-free technique and double mesh (P.H.S., Prolene Hernia System) (16). In recent years, we have used both of these techniques with excellent results and high patient satisfaction. However, "mesh and plug" is a more complicated technique, which requires dissection and identification of the spermatic cord and its vessels and therefore may be technically demanding, especially following multiple repairs of recurrent inguinal hernias. These problems can be avoided by using the open preperitoneal mesh repair method.

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Mean Blood Flow Velocities in Posterior Cerebral Arteries during Visual Stimulation

Marijana Lisak, M.D., Zlatko Trkanjec, M.D., Ph.D., Ivan Mikula, M.D., Ph.D., and Vida Demarin, M.D., Ph.D.

Abstract

Changes of mean blood flow velocities (MBFV) in the posterior cerebral arteries (PCA) recorded during visual stimulation in a group of 51 healthy, right-handed volunteers are presented. There were 27 (52.9%) males and 24 (47.1%) females, aged 20–59 years (mean age: 36.98 years). Measurements were performed with a hand-held 2 MHz transcranial Doppler (TCD) probe through the temporal window, with the subjects' eyes open and closed, and while they were looking at constant and at flashing white light. In half of the subjects, first the right PCA was insonated and then the left PCA, while in the other half the reverse procedure was used. Statistical analysis was done using Wilcoxon's matched-pair signed-rank test. Mean MBFV value in the left PCA was 41.2±8.6 cm/s (mean ± SD) with eyes open, 27.8±8.5 cm/s with eyes closed, 42.3±9.1 cm/s while looking at constant white light, and 43.0±9.6 cm/s while looking at flashing white light. Mean MBFV value in the right PCA was 41.7±8.9 cm/s with eyes open, 28.2±9.1 cm/s with eyes closed, 42.4±8.8 cm/s while looking at constant white light, and 43.4±9.2 while looking at flashing white light. Value differences for the left PCA, between eyes open and closed and between looking at constant white light and looking at flashing white light, were statistically significant ($p<0.001$, $z= -6.2146$, and $p<0.001$, $z= -3.4836$, respectively). For the right PCA, a value difference between eyes open and closed, and between looking at constant and flashing white light was statistically significant ($p<0.001$, $z= -6.2146$ and $p<0.001$, $z= -3.6928$), but there was no significant difference between eyes open and constant white light ($p=0.03$, $z= -2.1693$). The results showed that simple visual stimulation had an effect on blood flow velocities in PCA and that it could be measured with TCD.

Key Words: Posterior cerebral artery, visual stimulation, TCD.

Introduction

The primary visual fields of the cerebral cortex are located in both occipital lobes around the calcarine sulcus in Brodmann's area 17. The visual field is located mainly on the medial aspect of the occipital lobe, but at the apex of the occipital lobe the primary visual area extends partially into the lateral aspect of the occipital lobe. Around Brodmann's area 17, Brodmann's areas 18 and 19 function as associative visual areas, also called extracranial visual areas.

The brain receives arterial blood through the anterior (carotid) and posterior (vertebrobasilar) systems. The vertebrobasilar system consists of the left and right vertebral arteries, which fuse to form the basilar artery. The basilar artery, after a short course, divides into the right and left posterior cerebral arteries. The posterior cerebral arteries (PCA), emerging at the basilar artery bifurcation, provide arterial blood supply for most parts of the occipital lobe. Primary and associative visual areas located in the occipital lobe also receive arterial blood by way of the posterior cerebral arteries (1, 2).

In 1982 Rune Aaslid (3) described an original method of visualizing and measuring blood flow velocities in the arteries at the base of the brain. This method, named transcranial Doppler (TCD), has several advantages over other methods of cerebral blood flow visualization and measurement. Cranial bones pose a barrier for intracranial ultrasound Doppler examination, because they weaken ultrasound waves. The problem of ultrasound weakening has been solved by using low-frequency (2 MHz), pulsed ultrasound, and by placing the probe on the thinnest part of the temporal bone, right over the zygomatic arch (the so-called temporal window). The reflected ultrasound waves have an acceptable signal-to-noise ratio.

TCD is noninvasive, harmless, painless, and relatively inexpensive. It provides data in real time and has optimal time resolution of the measurement. Measurement can be performed for as long and as frequently as needed. In recent years, TCD has been gaining more importance in the evaluation of cerebral hemodynamics, and it has many areas of diagnostic and research applications. TCD enables one to perform measurement of the effect

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From the University Department of Neurology, Sestre milosrdnice University Hospital, Zagreb, Croatia.

Address all correspondence to Marijana Lisak, M.D., University Department of Neurology, Sestre milosrdnice University Hospital, Vinogradska 29, HR-10 000 Zagreb, Croatia; e-mail: marijana.lisak@zg.htnet.hr

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of any mechanical manipulation or functional stimulation on intracranial circulation (4, 5), and has been used to measure blood velocities in basal cerebral arteries during functional stimulation of distinct brain regions (reading, writing, cognitive tasks, visual stimuli, etc.). Different functional tests and pharmaceutical substances have been used during TCD monitoring to assess the cerebral circulatory reserve (hypercapnia, hypoxia, acetazolamide, etc.) (6).

Systolic, diastolic and mean blood flow velocities are used to describe the flow in basal cerebral arteries. However, mean blood flow velocity (MBFV) has a greater physiological significance, since it has the least dependency on cardiovascular factors such as cardiac frequency and contractility, peripheral resistance, and aortic elasticity. Also, MBFV has a closer time correlation with perfusion than other values (7, 8).

Subjects and Method

Measurements of MBFV in the posterior cerebral arteries during simple visual stimulation in healthy volunteers are presented. Measurements of mean blood flow velocities of the posterior cerebral arteries were performed on 51 healthy right-handed volunteers, with a hand-held 2 MHz probe using a Transscan 3D EME TCD device, at the Laboratory of Cerebrovascular Diagnosis, University Department of Neurology, Sestre milosrdnice University Hospital in Zagreb, Croatia.

PCAs were identified and insonated[1] through the temporal window using a standard technique (9), while subjects had their eyes wide open and then closed; mean MBFV in the PCAs was measured. Then the subjects watched a rectangular source of white light (constant white light) placed at a distance of one meter in front of them for one minute; and MBFV in each PCA was measured. After a resting phase of two minutes, the light was turned on and off every second (flashing white light) for one minute; MBFV in each PCA was measured. In half of the subjects, the measurements were first performed on the right side and then on the left side, while in the other half, the measurements were first performed on the left side and then on the right side. Thus, each subject had MBFV measurements done in the right and left PCA with eyes wide open, eyes closed, and while looking at constant and at flashing white light.

Statistical analysis was done using nonparametric Wilcoxon's matched-pair signed-rank test, and analysis of variance was done with Bonferroni correction. Differences were considered statistically significant at a p value of less than 0.01 ($p<0.01$). Results are presented as mean ± two standard deviations (SD).

Results

The study group consisted of 51 healthy right-handed volunteers, 27 (52.9%) men and 24 (47.1%) women, aged 20–59, mean age of 36.98 (SD=10.43) years.

MBFV in the left PCA was 41.2 ± 8.6 cm/s with the subjects' eyes wide open. Closing the eyes caused a drop of MBFV to 27.8 ± 8.5 cm/s, i.e., to 67.5% of the MBFV when their eyes were wide open. Wilcoxon's matched-pair, signed-rank test and analysis of variance with Bonferroni correction showed this difference to be statistically significant. While the subjects were looking at constant white light, MBFV was 42.3 ± 9.1 cm/s, i.e., 102.7% of the MBFV when their eyes were wide open, and while they were looking at flashing white light, MBFV was 43.0 ± 9.6 cm/s, i.e. 104.4% of the MBFV when their eyes were wide open. The differences for constant and flashing white light were found to be statistically significant with Wilcoxon's matched-pair, signed-rank test, but analysis of variance with Bonferroni correction did not show statistical significant difference. In the left PCA, the increase in MBFV while subjects were looking at constant white light was approximately twelve times smaller than the decrease in MBFV while they closed their eyes (2.7% to 32.5%). While they were watching the flashing white light, the increase in MBFV was approximately seven times smaller than the decrease in MBFV while the subjects closed their eyes (4.4% to 32.5%) (Table 1).

MBFV in the right PCA was 41.7 ± 8.9 cm/s when the subjects had their eyes wide open. Closing the eyes caused a drop of MBFV to 28.2 ± 9.1 cm/s, i.e., to 67.6% of the MBFV when they had their eyes wide open. Wilcoxon's matched-pair, signed-rank test and analysis of variance with Bonferroni correction showed this difference to be statistically significant. While the subjects were looking at constant white light, MBFV was 42.4 ± 8.8 cm/s, i.e., 101.7% of the MBFV when their eyes were wide open; and while looking at flashing white light, MBFV was 43.4 ± 9.2 cm/s, i.e., 104.1% of the MBFV when their eyes were wide open. The difference for constant white light was not statistically significant, with both Wilcoxon's

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[1] Insonation is the method used in Doppler ultrasound in which the angle between the Doppler ultrasound beam and the direction of blood flow in the vessel is examined by means of Doppler ultrasound probe.

TABLE 1

Mean Blood Flow Velocities in Left Posterior Cerebral Artery during Visual Stimulation

			Statistical Significance	
	Mean blood flow velocity mean ± 2 SD (cm/s)	**%**	**Wilcoxon's matched-pair signed-rank test**	**Analysis of variance with Bonferroni correction**
Eyes wide open	41.2 ± 8.6	100.0		
Eyes closed	27.8 ± 8.5	67.5	z = −6.2146 p < 0.001	t=14.008, p<0,001
Constant white light	42.3 ± 9.1	102.7	z = −3.4836 p < 0.001	t=1.201, ns
Flashing white light	43.0 ± 9.6	104.4	z = −3.7693 p < 0.001	t=2.102, ns

ns = non-significant

matched-pair, signed-rank test and analysis of variance with Bonferroni correction, while the difference for flashing white light was statistically significant with Wilcoxon's matched-pair, signed-rank test and not with analysis of variance with Bonferroni correction. In the right PCA, the increase in MBFV while subjects were looking at constant white light was approximately 19 times smaller (1.7% to 32.4%) than the decrease in MBFV when their eyes were closed. While watching the flashing white light, the increase in MBFV was approximately 8 times smaller than the decrease in MBFV while the subjects closed their eyes (4.1% to 32.4%) (Table 2).

There was no statistically significant difference in MBFVs between the left and right PCAs with the subjects' eyes wide open, closed, or while looking at constant or flashing white light, with both Wilcoxon's matched-pair, signed-rank test and with analysis of variance with Bonferroni correction (Table 3). However, distribution of values and results in all groups was not normal, i.e., distribution of all values and results was not Gaussian. Therefore, it was expected that parametric statistical analysis (analysis of variance with Bonferroni correction) would show only coarse, and not subtle, differences between groups. On the other hand, nonparametric statistical analysis (Wilcoxon's matched-pair, signed-rank test) showed only slight differences between groups.

Discussion

Vision is probably the most important sense in humans. And light is a stimulus that can be easily and precisely applied and controlled. Therefore, the application of light stimuli to the organs is a convenient method for performing different kinds of potentially important experimental research.

Many authors have recorded changes of blood flow velocities with TCD in the posterior cerebral arteries during visual stimulation (4, 10 – 15). Most of these studies report a decrease in blood flow velocities when the eyes were closed and an increase

TABLE 2

Mean Blood Flow Velocities in Right Posterior Cerebral Artery during Visual Stimulation

			Statistical Significance	
	Mean blood flow velocity mean ± 2 SD (cm/s)	**%**	**Wilcoxon's matched-pair signed-rank test**	**Analysis of variance with Bonferroni correction**
Eyes wide open	41.7 ± 8,9	100.0		
Eyes closed	28.2 ± 9.1	67.6	z = −6.2146 p < 0.001	t=14.802, p<0.001
Constant white light	42.4 ± 8.8	101.7	z = −2.1693, ns	t=0.837, ns
Flashing white light	43.4 ± 9.2	104.1	z = −3.6928 p < 0.001	t=1.909, ns

ns = non-significant

TABLE 3

Mean Blood Flow Velocities in Left and Right Posterior Cerebral Arteries during Visual Stimulation (Mean ± 2 Standard Deviations)

	Left PCA (cm/s)	**Right PCA (cm/s)**	**Statistical Significance**	
			Wilcoxon's matched-pair signed-rank test	**Analysis of variance with Bonferroni correction**
Eyes wide open	41.2± 8.5	41.7 ± 8.9	z= – 1.0867, ns	t=0.815, ns
Eyes closed	27.8± 8.5	28.2 ± 9.1	z= –0.9940, ns	t=0.0215, ns
Constant white light	42.3 ± 9.1	42.4 ± 8.8	z= –0.1688, ns	t=0.450, ns
Flashing white light	43.0 ± 9.6	43.4 ± 9.2	z= –0.8252, ns	t=0.622, ns

ns = non-significant

in velocities when the eyes were open as well as when various visual stimuli were used. However, the percentage of increase or decrease varies considerably according to different authors. Some of them recorded smaller, and others greater changes in blood flow velocities. These differences could be the result of the different methods of visual stimulation used by the various authors.

There are many mechanisms presumed to play a significant role in the autoregulation of cerebral blood flow, which is definitely increased by changes in metabolic activity. Cerebral blood flow is directly or indirectly coupled with the metabolic activity of the brain (vasoneural coupling). In many instances, significant differences in the regional cerebral blood flow may exist when distinct parts of the brain have increased metabolism (16, 17).

Since the visual cortex in the occipital lobes receives its blood supply almost exclusively from the posterior cerebral arteries, (2) all changes in the arterial blood flow due to differences in the metabolism of the visual cortex neurons are reflected in the arterial blood flow of the posterior cerebral arteries. Thus, changes in the blood flow of the posterior cerebral arteries could indirectly reflect changes in the metabolism of the visual cortex neurons. In the present study, MBFV was measured in the posterior cerebral arteries while the subjects were exposed to simple visual stimuli (opening and closing their eyes, and looking at constant and flashing white light). When their eyes were closed, there was a significant decrease of MBFV in the right and left posterior cerebral arteries. On the other hand, when they were looking at a constant white light, there was an increase in MBFV in both posterior cerebral arteries: in the left PCA, the increase was significant, while in the right PCA, the increase did not reach statistical significance. While they were looking at a flashing white light, there was a significant increase in MBFV in both PCAs.

These changes in MBFV support the concept of vasoneural coupling, i.e., the coupling of cerebral metabolism and brain blood flow. According to this concept, when the eyes are closed, the metabolism of the visual cortex significantly decreases, because there are fewer visual stimuli conducted through visual paths and therefore less visual information to process, thus explaining the decrease in MBFV recorded in the posterior cerebral arteries. On the other hand, when the eyes are looking at constant and flashing white light, there are more visual stimuli and therefore more visual information to process, thus enhancing the metabolism of the visual cortex, resulting in the increase in MBFV recorded in the posterior cerebral arteries.

However, the increase in MBFV, while the subject is looking at a constant white light was approximately 12–19 times smaller than the decrease in MBFV when both eyes were closed. The increase in MBFV while they were looking at a flashing white light was 7–8 times smaller than the decrease in MBFV when both eyes were closed. This could imply that most of the visual cortex neurons are metabolically active when the eyes are open, and that additional stimulation with constant white light causes only a slight additional increase in the metabolism of the visual cortex neurons. However, stimulation with a flashing white light caused an additional increase in MBFV, reaching statistical significance.

Also, from the results of this study it could be speculated that there might be some differences between the right and left occipital visual cortexes, since there was a statistically significant increase in MBFV in the left PCA, but not in the right PCA during stimulation with constant white light, but there was a statistically significant increase in MBFV in both PCAs during stimulation with a flashing white light. Also, it could be speculated that stimulation with a flashing white light could be more appropriate for detecting subtle changes in flow velocities in the PCAs. However, additional studies are needed to confirm these hypotheses.

This study showed TCD to be a very good method for measuring changes in the blood flow of basal cerebral arteries. TCD can measure changes in the brain activity in the area supplied by the posterior cerebral arteries indirectly, harmlessly and noninvasively, with high temporal resolution, as frequently and as long as necessary. These features make TCD an excellent method for the assessment of blood flow in the basal cerebral arteries.

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Nontyphoidal Salmonellosis and Mycotic Aneurysm:

A Case Report

Gian Marco De Marchis, M.D.[1], Marianne Braunschweig, M.D.[2], and Stefan Greuter, M.D.[3]

Abstract

A 74-year-old male with atherosclerosis presented with severe nontyphoidal salmonellosis, and received outpatient therapeutic antimicrobial treatment. Nevertheless, within seven days he developed a mycotic aortic aneurysm, a serious but treatable complication. Its surgical management was successful.

Rapid formation of mycotic aortic aneurysm represents a rare complication of a common disease, nontyphoidal salmonellosis. Atherosclerosis seems to be an important risk factor. Extensive work-up for mycotic aneurysm by CT-scan in patients older than 50 years, with nontyphoidal *Salmonella*-positive blood cultures, especially in the presence of risk factors for atherosclerosis, is prudent. However, blood and stool cultures of these patients can be negative in 15% and 35% of cases, respectively. And the results of the blood cultures may be delayed. So it is sensible to extend the previous recommendation to patients older than 50 years, with typical symptoms of nontyphoidal salmonellosis and imminent aneurysmatic rupture, independent of previous results of CT-scans, and blood or stool cultures.

Key Words: Nontyphoidal salmonellosis, atherosclerosis, mycotic aneurysm, CT, pancreatitis, antimicrobial treatment.

Introduction

NONTYPHOIDAL SALMONELLOSIS represents an important public health problem in the United States. About 1,400,000 cases of nontyphoidal *Salmonella* infection occur annually, resulting in approximately 15,000 hospitalizations and 400 deaths annually (1). In general, nontyphoidal salmonellosis is a self-limiting disease. The therapeutic cornerstone is replacement of fluids and electrolytes. Antimicrobial therapy plays a role only in severe cases (2) and as a pre-emptive treatment (3) (Table). Independent of the severity of the primary disease, pre-emptive treatment aims to prevent complications, such as mycotic aneurysm, endocarditis, and other prolonged infections, in high-risk patients.

TABLE

Criteria and Indications for Severe Nontyphoidal Salmonellosis and Pre-emptive Antimicrobial Treatment, Respectively. (Only in These Two Cases Is Initial Antibiotic Prescription Recommended.)

Criteria for severe nontyphoidal salmonellosis (2)

1. Presence of high fever
2. More than 9 stools per day
3. Need for hospitalization

Reasonable indications for pre-emptive antimicrobial treatment

1. Children younger than 1 year (3)
2. Patients older than 50 years with atherosclerosis
3. Immunocompromised patients with
    a. an organ transplant
    b. AIDS
    c. sickle cell disease or other hemoglobinopathies
    d. endovascular or osseous prostheses

Case Report

A 74-year-old man presented in April 2004, complaining of bloody diarrhea up to 10 times per day, and fever. He reported no vomiting. On examination, we found epigastric tenderness with regular bowel sounds. The digital rectal exam did not show any rectal abnormality. His axillar tempera-

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[1] Ospedale La Carità, Locarno, Switzerland, and Departments of [2] Radiology, and [3] Internal Medicine, Hospital Centre Biel, Switzerland.

The work originated from the Department of Internal Medicine, Hospital Centre Biel, Vogelsang 84, Postfach, 2501 Biel, Switzerland.

Address all correspondence to Gian Marco De Marchis, M.D., Ospedale La Carità, Via all'Ospedale 1, 6600 Locarno, Switzerland; e-mail: gmdemarchis@students.unibe.ch

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ture was 37.7°C (99.9°F). The laboratory studies revealed a C-reactive-protein (CRP) of 192 mg/L (normal < 5 mg/L), but no leukocytosis. The abdominal CT-scan displayed no irregularity explaining our patient's clinical condition. The abdominal aorta showed atherosclerotic changes; its size and surrounding fat tissue were normal (Fig. 1). We intravenously replaced fluids and electrolytes. Since we suspected severe bacterial enteritis, the outpatient therapy was based on oral rehydration and ciprofloxacin (250 mg bid).

Seven days later, the patient returned with severe abdominal pain, bilaterally radiating to the back. We saw a febrile, hypertensive, hemodynamically stable patient. The abdomen showed neither tenderness nor abdominal pulsations or murmurs. In the laboratory studies, CRP (271 mg/L) and lipase (566 U/L, normal 13 – 60 U/L) were elevated. Suspecting acute pancreatitis, we repeated the abdominal CT-scan. This time it showed a saccular, infrarenal, abdominal aortic aneurysm of a maximal diameter of 5 × 4 cm (Fig. 2). The enhancing of the periaortic fat tissue and mesenteric root were consistent with imminent aneurysmatic rupture or inflammation. Blood cultures grew *Salmonella enteritidis*. The patient received emergency surgical intervention. We diagnosed an acute mycotic infrarenal aortic aneurysm, and continued the antibiotic therapy with ciprofloxacin, at a higher dosage (400 mg IV tid, later 750 mg po tid). The patient successfully survived a surgical complication including a postoperative paresis of the right leg. When last contacted, in September 2004, he still presented some problems with ambulation. Nevertheless, his general condition was good.

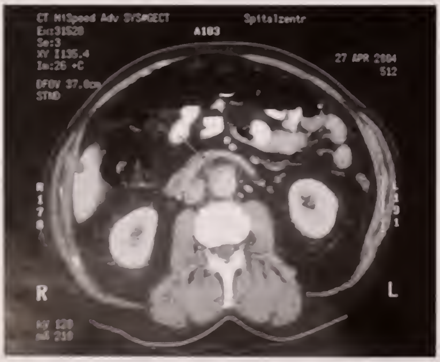

Fig. 1. Transverse abdominal CT-scan with contrast medium. Normal-sized abdominal aorta with atherosclerotic changes (see arrow).

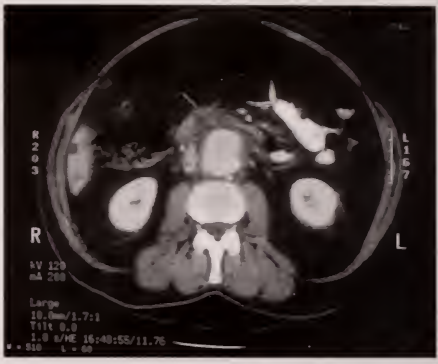

Fig. 2. Seven days later, the transverse abdominal CT-scan with contrast medium shows aneurysmatic dilatation of the abdominal aorta (see arrow).

Discussion

We present the rapid evolution of nontyphoidal salmonellosis to a mycotic aneurysm in just seven days. The first time we saw our patient he suffered from isolated enteritis. We had no clinical or radiological evidence of early aneurysmatic development. We offered him intravenous replacement of fluids and electrolytes. Since our patient suffered from severe (likely bacterial) enteritis, and showed atherosclerotic changes of the abdominal aorta, we prescribed antimicrobial treatment. One week later he complained of new symptoms, namely severe abdominal and back pain. These are common symptoms of a mycotic aortic aneurysm (4 – 6) and pancreatitis. Our patient's elevation of serum lipase activity without any radiological signs for acute pancreatitis is a known finding in nontyphoidal salmonellosis, often with no clinical significance (7). However, the diagnosed rapid formation of a mycotic aneurysm is an occasional complication of *Salmonella* infection, with a high mortality rate (4 – 6, 8). Five percent of patients with nontyphoidal salmonellosis develop bacteremia (9). Only 10% of patients older than 50 years with nontyphoidal *Salmonella* bacteremia develop vascular infection (10). As in our case, of these most patients have pre-existing atherosclerotic disease at the site of the subsequently infected aneurysm (4). The abdominal aorta, especially the infrarenal segment, seems to be the blood vessel most frequently involved. CT-scan is the preferred imaging modality. It is widely available and fast, and may depict early periaortic findings (soft-tissue mass, stranding and fluid) (6).

Treatment of a mycotic aneurysm consists of timely surgical intervention with prolonged antibiotic therapy (4–6). Some authors recommend extensive work-up for mycotic aneurysm in patients older than 50 years with nontyphoidal *Salmonella*-positive blood cultures, especially in the presence of risk factors for atherosclerosis (10). However, blood and stool cultures of these patients can be negative in 15% and 35%, respectively (4). And the results of the blood cultures may be delayed. So it is sensible to extend the previous recommendation to patients older than 50 years with typical symptoms of nontyphoidal salmonellosis and imminent aneurysmatic rupture, independent of previous results of CT scans, and blood or stool cultures.

In summary, a common disease such as nontyphoidal salmonellosis may on occasion rapidly evolve into a mycotic aneurysm, a potentially fatal, but treatable complication. Its diagnosis remains a challenge—a challenge every physician may face.

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Organophosphate Poisoning Associated with Fetal Death:

A Case Study

Ahmet Sebe, M.D.[1], Salim Satar, M.D.[1], Rana Alpay, M.D.[1], Nalan Kozaci, M.D.[1], and Ahmet Hilal, M.D.[2]

Abstract

The increasing use of organophosphorus insecticides in agriculture and inside homes and schools, as well as its widespread existence in the environment, poses a potential health hazard. As the use of these agents increases, acute and chronic exposure has become more common. As with other organophosphates, chlorpyrifos kills insects and other animals, including human beings, because of its toxicity to the nervous system. Exposure of pregnant women to organophosphates is an important clinical entity because of its effects on two organisms—mother and fetus. There are few reports about fetal toxicity of organophosphates in the literature because of the relatively few cases reported. In this paper we report a case of intoxication from chlorpyrifos, an organophosphorus compound, during pregnancy, causing fetal death.

Key Words: Abortion, chlorpyrifos, organophosphates, poisoning, pregnancy.

Introduction

Organophosphate compounds used as pesticides in agriculture are toxic not only to pests, but also to humans, whether through unintentional exposure or, especially, in suicide attempts.

Despite the widespread use of pesticides, and the fact that studies have investigated the mechanism, clinical findings, diagnosis, treatment and prognosis of the poisoning, little is known about potentially adverse effects *in utero* resulting from exposure of pregnant women to pesticides (1) due to the relatively few reports in the literature and the prohibition on evaluating the disease experimentally in pregnancy. The data found in the literature include few case reports of intoxicated pregnant women and limited animal studies. This case study covers intoxication from chlorpyrifos, an organophosphate compound, causing the death of a fetus because of delay in therapy of the mother (who was treated successfully).

Case

A 23-year-old primigravida female was brought to the emergency department (ED) after taking an excessive amount of chlorpyrifos-ethyl (Sarban 2 dust®) in an attempted suicide 12 hours previously. She had been taken to a rural hospital at first because she could not feel her baby's movements in the second hour after ingestion of the substance. She was hospitalized for 8 hours after gastric lavage. Then she was transported to our center after being diagnosed by fetal ultrasonography, with *in-utero* death of the fetus at gestation age of 19 weeks. (Her relatives had brought the bottle of the chemical to the hospital.) Her medical history revealed nothing significant. Her initial vital signs were as follows: blood pressure, 120/90 mm Hg; pulse, 120 beats/min; respiratory rate, 15 breaths/min; and axillary temperature, 36.7°C. Physical examination revealed a palpable uterus 2 cm under the umbilicus, fasciculation at her tongue, and miosis. There was no lacrimation, excessive urination, emesis, or bradycardia. Other systems examined were normal. Her laboratory tests were as fol-

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From the Departments of [1]Emergency Medicine and [2]Forensic Sciences, Cukurova University School of Medicine, Balcali, Adana, Turkey.

Address all correspondence to Ahmet Sebe, M.D., Cukurova University, School of Medicine, Department of Emergency Medicine, 01330 Balcali, Adana, Turkey; email: asebe@cu.edu.tr

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lows: white blood cell, 6,700 μL (normal range: 4,300–10,300μL); Hgb, 10.2 g/dL (13.6–17.2 g/dL); Hct, 30.3% (39.53–50.33%); platelets, 240,000/μL (156,000–373,300/μL); plasma cholinesterase, 39 U/L (5,500–12,000 U/L); glucose, 78 mg/dL (70–105 mg/dL); BUN, 7 mg/mL (8–25 mg/mL); creatinine, 0.5 mg/dL (0.8–1.2 mg/dL); Na, 139 mmol/L (135–145 mmol/L); K, 3.5 mmol/L (3.5–5.1 mmol/L); ALT, 28 U/L (<41 U/L); AST, 30 U/L (5–40 U/L); LDH, 475 U/L (160–500 U/L); creatine kinase, 39 U/L (<170 U/L); and amylase, 43 U/L (28–100 U/L). A 12-lead electrocardiogram revealed sinus tachycardia.

As soon as the patient was admitted to the ED, two 18-gauge catheters were inserted and supplemental oxygen was administered at the rate of 4 L/min. Cardiac and pulse oxymetric monitoring were also initiated. Fluid replacement was initiated as 3,000 mL/m^2/day. After intravenous (IV) 10 mg metoclopramide administration, gastric lavage was performed and charcoal was given through a nasogastric (NG) tube, at a dose of 1 g/kg. Atropine sulfate 10 mg IV bolus following 60 mg infusion/day was started. Simultaneously, IV 2 gr 2-PAM (pralidoxime) was given for 20 minutes in the other arm. An Obstetrics and Gynecology Department consultation was obtained for the patient's pregnancy and fetal condition. Obstetric ultrasonographic results revealed no cardiac activity of the fetus, whose biparietal diameter matched gestational age of 18 weeks 5 days. At the advice of the obstetrician, 200 mg of misoprostol was given intravaginally. Twelve hours later, she delivered the fetus by normal vaginal route. A curettage was performed for placenta residue. Autopsy and histopathological examinations were performed.

The follow-up of the patient was done by our clinic in the observation unit. Atropine infusion therapy continued for four days, and daily plasma pseudocholinesterase levels were monitored for enzyme regeneration. Her plasma pseudocholinesterase levels were not remarkably elevated (day 2: 42 U/L, day 3: 31 U/L, day 4: 51 U/L, discharge day 7: 52 U/L); no cholinergic symptoms were detected and atropine infusion was gradually stopped. She was given 2 packages of erythrocyte suspension because of vaginal bleeding after curetage (resulting in a decrease in hematocrit level) on the second day of hospitalization. On the fifth day of hospitalization, she had fever with a bad odorous vaginal discharge. Endometritis was diagnosed and proper antibiotherapy was initiated. She did not have any symptoms of toxicity, and so she was started on oral feeding. The patient was discharged 7 days after admission. One week later, she was referred for gynecologic and psychiatric therapy.

The body measurements of the fetus, with male external genitalia, according to the autopsy report, were as follows: body length, 25.5 cm; weight, 410 grams; head circumference, 17.5 cm; chest circumference, 14.5 cm; abdominal circumference, 14 cm; and length of the foot basis, 3 cm. The autopsy report listed the fetus as having an estimated gestational age of 19 weeks, based on anthropological measurements. The fetus had traumatic lesions, tool wounds or morphological defects. A blood sample of the fetus was analyzed with the Agilent GC/MS device (Hewlett Packard, with liquid-liquid extraction method). The result revealed the presence of a chemical, 264 ppb chlorpyrifos, which is an organophosphate insecticide.

Discussion

Organophosphates, a widely used class of insecticidal compounds, have been shown to cross the placental barrier and thus potentially affect the developing fetus (2). The toxicological effect of chlorpyrifos has been studied extensively. According to Environmental Protection Agency (EPA) guidelines of the United States, chlorpyrifos has been shown not to be mutagenic (3), carcinogenic (4) or teratogenic (5). Breslin et al. evaluated its potential to produce developmental and reproductive toxicity in rats and showed that oral administration of chlorpyrifos to pregnant rats at parentally toxic dose levels was not embryolethal, embryo-fetotoxic, or teratogenic, and did not adversely affect fertility or the function or the structure of the reproductive organs (6).

In tests conducted by Dow Chemical, feeding chlorpyrifos at high doses to pregnant mice caused them to give birth to small pups with an increased incidence of skeletal abnormalities. At a lower dose, the same study found an increase in skull defects that allowed the brain to be exposed (7). In 1993, chlorpyrifos was claimed to cause neurologic disorders in humans, with *in utero* exposure, when a family had two babies with similar neurologic problems such as cerebral palsy, cataracts and seizures. It was learned that the parents were using a chlorpyrifos-containing pesticide to kill ticks to protect their first baby from Lyme disease. When their second and third babies were born with neurologic abnormalities, the doctors agreed that *in utero* exposure might have affected the mother and caused the diseases (8). Chlorpyrifos was detected in cervical mucus, sperm fluid, and human milk by German researchers, findings that suggest its serious effects on human reproduction (9).

Our patient's report of not feeling her baby's movements 2 hours after ingestion of the toxic substance, plus the autopsy findings of suppressed maternal serum pseudocholinesterase levels, high levels of chlorpyrifos detection in fetal blood and lack of any macroscopic anomalies, lead us to conclude that chlorpyrifos is fetotoxic and that it may have been the cause of fetal death in this case. Based on our experience with the follow-ups of other pregnant intoxicated patients, we conclude that early recognition and treatment of organophosphate intoxication in pregnant women can be managed successfully without any abortion or fetal death, and that healthy babies can be delivered. We have had three other pregnant patients with organophosphate intoxication in the last five years, all of whom received medical therapy immediately after admission. One of the fetuses was in the 20th week of gestation, the other two were near term. All three women gave birth to healthy babies. The follow-ups of the babies were also normal and the oldest one is a healthy 4-year old girl today. We could not determine the name of the organophosphate compounds of those previous intoxications and of course chlorpyrifos may not have been the toxic substance. But we think that for this patient, late admission to a medical center and delay in medical therapy (2-PAM and atropine) may have been the reasons for fetal loss. The mechanism of the fetal death may have been fetal bradycardia and/or placental insufficiency because of maternal bradycardia. These suggestions should be investigated and new experimental studies need to be designed.

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Eric Widera and Roxana Sulica
Mount Sinai School of Medicine

The Role of High-Density Lipoprotei Cholesterol in Atherothrombosis
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Commencement Address
May 2005

IT IS AN ENORMOUS PRIVILEGE to stand before you today. As you know, it is a commencement for all of us, and a parting with its bittersweet emotions. June 2, 1976 was my graduation day from medical school, and in preparation for this talk I decided to try and remember who gave the commencement speech. Well, I have no memory of it whatsoever. I eventually found the program, and it was the then-mayor of New York, Mr. Abe Beame. So I called the people at NYU and asked what he said that day. No one knew. I wondered if there was there any record. I looked in the *New York Times* for the following day: nothing. So I have a challenge here. My challenge is to see that 25 years from now you will at least remember that I spoke to you today.

William Osler is quoted as asking medical students at Johns Hopkins, in the early 1900s, on their first day, "Are you tough enough to be doctors?" I would ask all of you today, "Do you have the courage to move into the world that we are all facing?" The often-quoted opening of Charles Dickens's novel, "It was the best of times, it was the worst of times," seems always relevant to medicine and perhaps never more than today.

It is amazing that today, when doctors have such effective tools of diagnosis and therapy, and can truly change the course of human disease, we find ourselves in such a quagmire as a profession. Biomedical science has the tools to answer many questions at the molecular and atomic level, and yet the funding for research may be decreasing, the political interference in biomedical research is increasing, and people are demanding of physicians and researchers to prove the value for the dollars being spent. This is indeed a new world.

One thing that has happened in this new world and that it is very sad for all of us, is that there has been a general loss of trust. Without trust by all who relate to medicine, medicine is a very difficult profession. Ask yourself why, with all this potency of diagnosis and therapy, patients seem disgruntled. They cannot easily get to see the doctor. More and more patients are disenfranchised from our health care system. Doctors do not seem to be listening. Five-minute visits after months of waiting are not satisfactory. The doctors seem disgruntled. There is early retirement. There is early burnout. The people who pay for care are convinced they are not getting their money's worth.

What is going on? The ability to deliver effective care has not translated into professional satisfaction for anyone.

We have the ability to prevent disease, understand the etiology of every common ailment almost at the molecular level, and yet we have an epidemic of obesity, diabetes, and heart disease. The prevention of many types of cancer is readily attainable, yet such prevention is rare, because, among other reasons, some people are uninsured and do not get preventive care, and many medical practices have never instituted the systems necessary to really deliver good preventive care. We have a technologically supercharged health care system, and yet patients are crying out that no one listens to them. The health care system in this country is spending money like never before, yet more and more people do not even receive health care. The world is ready to spend trillions of dollars on weapons, and yet the continent of Africa is being ravaged by a disease for a lack of medication that would cost a thousandth of that amount.

You really have a lot of challenges, so let's reflect. Let's think about this whole idea of commencement, because "commencement" is an interesting word. Yes, it means beginning, but we know that this is more than a beginning today. Today is an end of one part of your life and the beginning of another. You came here wearing Birkenstocks and ragged t-shirts, and thought you were really fantastic. You were the envy of everyone. Then you were transformed over four years, and today the crowning glory of that transformation is that henceforth people will call you doctor. And that is a heavy load. There is a lot that goes with being a doctor. You receive instant credibility and instant prestige from the entire world around you. You sometimes can't stop people from calling you doctor. You wonder if, for a moment, you can stop being a doctor. But you can't. Being a doctor is

24/7, and people understand that. They understand that you are not the same person you used to be. You see the world as a doctor does. You relate to people as a doctor does, and you have responsibilities 24/7, the way a doctor does.

Although you receive lots of benefits, this is not a one-way street; it is really a social contract. If you accept this role and you really allow the personal transformation to happen, special things follow. People let you inside their private lives in a way that they let no one else. Every day that I see patients, I am in awe of what I learn from them and this unique privilege they grant me. Let me tell you one story, because, as you know, I love telling stories.

A story of one day, when I was startled by being let inside the magic of someone's life. I was making a house call to a woman who was dying of an abdominal tumor. She had a bowel obstruction, but she didn't want to go to the hospital; in fact, she was clearly coming to the end of her life. I had spent many hours talking to her about her medical history. That day I drove out to her house, where she was being cared for by her 90-year-old mother. She and the mother had emigrated from Greece years earlier.

I went in and sat with her, and we talked about pain control and her symptom management and how it was getting close to the end. She said to me at the end of our talk, "Dr. Smith, I lied to you, and I need to set it right." I said, "OK, what did you lie to me about?" I couldn't imagine any untruth that was really relevant to this woman who was withering away in front of my eyes. She replied, "Take the picture from the end table." It was a photo of her mother. She said, "Open the back of the picture." Out dropped another photo, one of her and a young man when they were probably about 20 years old. She said, "Remember, you kept asking me if I ever had another person in my life, if I had been married, and I kept telling you, no, no, no? Well, you are now the only person who knows."

She then told me a story of what it was like to live in a small village in Greece during the Nazi occupation and how incredibly euphoric it was when the Americans liberated her town. She told me how she fell in love with an American soldier and had a wild love affair that lasted all of three weeks, until his unit moved on. She never saw him again, and all she had from that affair was this picture hidden behind her mother's, and no one had ever seen it except her. She said she wanted to make sure I knew all about her before she died.

I remember driving home that day wondering, am I really ready for this? If people are going to let me that deep into their personal lives, I'd better be pretty respectful and I'd better remember what a privilege this is.

Now, you are all going to be moving on to the next step of your careers, and you are going to be busy. You are going to be mastering medicine and you will soon be the masters of the universe of medicine. You will know all the high tech stuff. You will know what tests to order and how to organize your workday. But let me give you some advice.

Don't cheat yourselves. Medicine is not really about technology and tests. It is not even about the income. Medicine is all about the patients. So promise me something. Every single day of your life, with at least one patient, put the brakes on. Stop. Sit down and learn who that person is. Just calmly sit and have a conversation and remind yourself that the privilege of doctoring has all of its roots in the sanctity of the relationship between you and your patients. It can never be a job. It can never be a business. It is always a sacred trust, and all the respect you will get for the rest of your life stems from your being true to that trust.

Medicine is also a field of action. It doesn't matter that you know things. It only matters if you *do* things. And when you do them, you have to be effective. And to be effective, people have to trust you and believe in you. Being a successful physician is not primarily about being right or about being smart. By the end of your career, people are going to benchmark your success not by whether you can pass a test, but by whether the patients entrusted to your care did well. Never lose sight of that benchmark.

I truly believe that you have to take care of yourselves. You have to be parents, husbands, and wives. You have to have a life outside of medicine, but don't think that striking a balance in your life in any way stops you from deeply falling in love with taking care of patients and being a doctor.

We have to be grateful to all our teachers—our professors, our parents, out mentors. But never forget that the teachers who teach you the most may be your patients, and you need to be eternally grateful that they put their trust in you, novice physicians learning the craft of medicine by practice.

Let me conclude with a wish for all of us. That wish is that we take care of ourselves, that we as a profession love one another, that we take care of our patients and do good, and that we have a life of joy in doing so.

Good luck and congratulations.

Lawrence G. Smith, M.D.
Chief Academic Officer and
Senior Vice President of Academic Affairs
North Shore Long Island Jewish Health System
Great Neck, NY

Grand Rounds

Pulmonary Artery Sarcoma Misdiagnosed as Chronic Thromboembolic Pulmonary Hypertension

Eric Widera, M.D.[1], and Roxana Sulica, M.D.[2]

Abstract

Pulmonary artery sarcomas are rare neoplasms of the pulmonary artery that are often confused with chronic thromboembolic disease, as both diseases have similar presentations. In patients with presumed chronic thromboembolic pulmonary hypertension, certain clinical and imaging characteristics may suggest the alternative diagnosis of pulmonary artery sarcoma. In this article we present a case of a man initially diagnosed with chronic thromboembolic pulmonary hypertension, but who was later found to have pulmonary artery sarcoma. We review the distinguishing characteristics of the two diseases and discuss possible treatment strategies.

Key Words: Pulmonary artery sarcoma, chronic thromboembolic pulmonary hypertension, ventilation-perfusion scan, computed tomographic angiogram.

Case Report

A 66-year-old man with a history of mild chronic obstructive pulmonary disease and heavy tobacco use was initially admitted to an outside hospital with a 3-month history of dyspnea and cough. He was placed on heparin for a presumptive diagnosis of pulmonary embolism based on a computed tomographic (CT) scan of the chest, which showed a "filling defect" in the main pulmonary artery extending into and completely occluding the left pulmonary artery. A ventilation-perfusion scan showed normal ventilation with complete lack of perfusion to the left lung and entirely normal perfusion of the right lung. The work-up for hypercoagulable state was negative. The patient subsequently received warfarin anticoagulation and Greenfield filter placement, and was discharged home.

One month later he developed small amounts of hemoptysis. A repeat CT scan revealed an increase in the size of the "filling defect" in the pulmonary artery. Transthoracic echocardiography showed elevated right ventricular systolic pressure (RVSP) of 65 mm Hg and mild right ventricular dysfunction. The patient was referred to the Mount Sinai Pulmonary Hypertension Program for further management, still complaining of chronic dry cough and intermittent hemoptysis, and having lost 25 pounds over a 3-month period. On physical examination the patient's blood pressure was 135/75 mm Hg, with a heart rate of 85 beats/min, and oxygen saturation of 97% in room air. Fine rales were audible at the left lung base, while the cardiovascular examination was normal. The chest radiographic examination was significant for prominence of the main pulmonary artery and an ill-defined nodular density in the left mid-lung field. Ventilation-perfusion scanning again demonstrated complete lack of perfusion to the left lung with normal ventilation (Fig. 1). A repeat chest CT angiogram showed further interval increase in the pulmonary artery "filling defect," with total occlusion and invasion of the wall of the left pulmonary

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[1]Resident and [2]Assistant Professor of Medicine, Cardiovascular Institute, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Roxana Sulica, M.D., Mount Sinai Pulmonary Hypertension Program, Box 1030, One East 100th Street, New York, NY 10029; email: Roxana.Sulica@mountsinai.org

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on June 29, 2004, and updated as of May 2005.

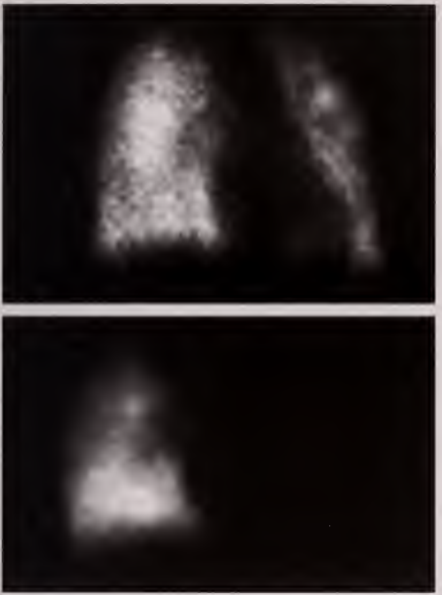

Fig. 1: Upper image: ventilation scan. Lower image: perfusion scan. Anterior views, showing lack of perfusion and normal ventilation on the left.

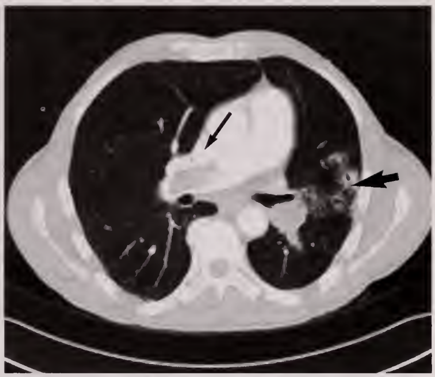

Fig. 2: CT chest examination showing large pulmonary arterial mass (thin arrow), mediastinal lymphadenopathy and left upper lobe infiltrate (thick arrow).

artery and extension into the right upper lobe anterior segment associated with a left upper lobe cavitary mass with surrounding infiltrate (Fig. 2). Echocardiography showed mild right ventricular dilatation with probable normal function, but RVSP could not be estimated due to insufficient tricuspid regurgitation. The patient was restarted on heparin and received antibiotics for possible community-acquired pneumonia. Three induced-sputum specimens failed to disclose acid-fast bacilli.

Given the progression of the pulmonary arterial "filling defect" despite long-term anticoagulation, the pulmonary artery mass extension into the vascular wall, and the unilateral character of the lung perfusion defect in a patient with symptoms of chronic disease, the possibility of a pulmonary artery sarcoma was entertained. The patient was referred for surgical consultation. Preoperatively, pulmonary function tests were significant only for mild obstructive flow pattern, and left heart catheterization showed evidence of non-obstructive coronary artery disease. The patient underwent surgery with partial resection of a bilateral pulmonary artery tumor. There were no complications from the procedure. Pathology revealed high-grade spindle cell sarcoma consistent with leiomyosarcoma. There was no evidence of lung metastasis, and the nodular left upper lobe mass proved to be a lung infarct. The patient was discharged from the hospital 6 days after surgery, but no chemotherapy was instituted, in accordance with the patient's preference. Eighteen months after surgery the patient is alive and well.

Discussion

As this case exemplifies, the preoperative diagnosis of pulmonary artery sarcoma is difficult and frequently delayed, as it is often confused with chronic thromboembolic disease. In the initial evaluation of patients with presumed chronic thromboembolic pulmonary hypertension (CTEPH), certain presenting aspects may suggest an alternative diagnosis of a pulmonary artery neoplasm. We will briefly review the diagnostic criteria and the work-up of CTEPH and discuss those diagnostic clues that should alert physicians to the uncommon entity of pulmonary artery sarcoma. For both conditions, surgery is the only treatment modality with curative potential. A presumptive preoperative diagnosis of a pulmonary artery neoplasm rather than chronic thromboembolic disease may influence the operative technique. The long-term prognosis is better for chronic thromboembolic disease compared to pulmonary artery sarcoma, even if complete resection is feasible.

Chronic Thromboembolic Pulmonary Hypertension

Chronic obstruction of the main pulmonary arteries due to unresolved thromboembolic disease is an often underdiagnosed but potentially correctable cause of pulmonary hypertension, and a relatively common and serious complication of pulmonary embolism. In a recent prospective case series, the cumulative incidence of pulmonary hypertension after one episode of an adequately treated acute pulmonary embolism in patients without a history of prior venous thromboembolism was 1% at 6 months, 3.1% at 1 years, and 3.8% at 2 years (1). However, in clinical practice most patients present late in the course of the disease, as many patients may remain asymptomatic for months or even years.

The pathogenesis of pulmonary hypertension in chronic thromboembolic disease is multifactorial. In the majority of patients, more than 40% of the pulmonary vascular bed is obstructed by organized thrombi (2), but other factors, such as recurrent thromboembolism, in-situ pulmonary artery thrombosis, and pulmonary vascular remodeling with the development of a hypertensive pulmonary arteriopathy, play a significant role in the hemodynamic progression of the disease (3, 4).

The clinical signs and symptoms of chronic thromboembolic pulmonary hypertension, such as progressive exertional dyspnea and decreased exercise tolerance, mimic those of other forms of pulmonary hypertension. As the disease progresses, chest pain on exertion, presyncope, or syncope may occur. Findings on physical examination include an accentuation of the pulmonic component of the second heart sound. In some patients, a bruit over the lung fields may be heard; it originates from turbulent pulmonary blood flow through partially occluded pulmonary arteries by recanalized thrombi (5).

As with pulmonary hypertension of all types, the diagnostic work-up includes determination of the disease severity, assessment of right ventricular function and a thorough search for other conditions known to be associated with pulmonary hypertension. When CTEPH is suspected, certain imaging modalities are employed to establish the proximal extent and location of the thromboembolic material; these variables are the most important determinants of the operative candidacy (2). Transthoracic echocardiography often demonstrates impaired right ventricular systolic function with enlargement of the right atrium and right ventricle and moderate-to-severe tricuspid regurgitation (6). Ventilation-perfusion scanning should be performed in all patients with pulmonary hypertension to screen for the presence of chronic thromboembolic disease. Any mismatched, segmental or larger perfusion defects would help to differentiate chronic thromboembolic pulmonary hypertension from pulmonary arterial hypertension, as there should be no large perfusion defects in the latter (7). Lower extremity Doppler examination may also be performed, but evidence of prior deep vein thrombosis is only seen in 35–45% of patients with CTEPH (8, 9). Findings on chest CT examination include presence of chronic thromboembolic material located in an eccentric position within the central pulmonary arteries, bronchial artery collateral flow, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma (2).

Pulmonary angiography is the definitive test to characterize the surgical operability of CTEPH; it is recommended for all patients with suggestive ventilation-perfusion scans. Pulmonary angiographic findings in CTEPH include "pouching" defects, webs or bands, abrupt vascular narrowing, complete vascular obstruction, and intimal irregularities. The latter finding is in contrast to the well-defined intraluminal defects seen in acute embolisms (10). In specialized centers, direct visualization of the intimal changes of the pulmonary artery may be done at angioscopy (2). Right heart catheterization is performed in all patients with unexplained dyspnea, large mismatched perfusion defects and evidence of pulmonary hypertension and right ventricular dysfunction (2), since hemodynamic parameters, particularly the calculated pulmonary vascular resistance, are important factors in the preoperative evaluation.

The prognosis of patients with CTEPH is poor without intervention and depends on the degree of pulmonary hypertension at the time of diagnosis. The five-year survival rate is reported to be 30% if pulmonary artery pressure is greater than 40 mm Hg and only 10% if pulmonary artery pressure is above 50 mm Hg (8). Definitive treatment includes the use of lifelong anticoagulation, inferior vena cava filter placement and the use of pulmonary thromboendarterectomy in selected symptomatic patients with hemodynamic or ventilatory impairment at rest or with exercise. Pulmonary thromboendarterectomy is a true endarterectomy that involves removal of the organized fibrotic material in the large pulmonary vessels. The procedure is performed through median sternotomy, with cardiopulmonary bypass under deep hypothermia and periods of hypothermic circulatory arrest (11). Both short- and long-term surgical results are excellent in specialized centers with large operative volume, with reported mortality for thromboendarterectomy as low as 4.5% (12). These results compare favorably with outcomes from lung transplantation, which is the only surgical alternative. For CTEPH patients with inoperable disease, chronic administration of pulmonary vasodilators commonly used for pulmonary arterial hypertension may offer symptomatic and functional benefit, but, to date, no large-scale studies have been performed with such patients (13, 14).

Pulmonary Artery Sarcoma

Pulmonary artery sarcomas are rare tumors. The first such case was reported in 1923 (15), and since then, approximately 150 primary sarcomas of the pulmonary artery have been described (16). Most pulmonary artery sarcomas are classified as undifferentiated spindle cell sarcomas or leiomyosarcomas, but the histological classification does not appear useful prognostically or clinically (17). The usual duration of symptoms before presentation is around 3–12 months. Clinical presentation includes dyspnea, chest or back pain, cough, and hemoptysis, as well as signs and symptoms of pulmonary hypertension and right ventricular dysfunction. These clinical findings may mimic those of chronic thromboembolic pulmonary hypertension, but a history of weight loss, clubbing, low-grade fever, anemia and an elevated ESR should raise suspicion of malignancy (17). Other warning signs include lack of prior history of deep vein thrombosis or pulmonary embolisms, a negative work-up for a procoagulant state, and no response to anticoagulation over several weeks (17).

Pulmonary artery sarcomas and chronic thromboembolic pulmonary hypertension are easily confused by CT scan findings because both diseases have intraluminal filling defects and pulmonary arterial dilation, but there are radiographic criteria that may help differentiate the two entities. CT findings consistent with malignancy include filling defects occupying the entire luminal diameter of the main or proximal pulmonary arteries, expansion of the involved pulmonary artery with the filling defect, and extraluminal extension of the tumor (18). In addition, pulmonary artery sarcomas may be indicated by areas of inhomogeneous high or low attenuation representing hemorrhage or necrosis, soft tissue density in pulmonary arteries, or enhancement after administration of gadopentetate dimeglumine on magnetic resonance imaging examination (19). A unilateral central pulmonary embolus is relatively uncommon and suggests the possibility of malignancy.

Ventilation/perfusion scans may demonstrate perfusion defects of varying size in one or both lungs with pulmonary artery sarcomas. Predominantly unilateral perfusion defects are rare in CTEPH and suggest malignancy. Otherwise, the perfusion defects are indistinguishable from pulmonary embolism, but serial scans will show no resolution despite anticoagulation, as seen in the case presentation. Pulmonary angiography may show intraluminal masses and lung perfusion abnormalities with a smooth tapering of pulmonary arteries and "to-and-fro" motion of pedunculated or lobulated lesions (17).

The prognosis of pulmonary artery sarcomas is extremely poor. The median survival of untreated patients is as short as one and a half months, with decompensated heart failure as the primary cause of death (20–22). Metastases are primarily to the lung, while distant extrathoracic metastases develop in 16% of cases. Treatment with aggressive resection lengthens median survival time to 10 months, with rare reports of patients remaining tumor-free 5 years after the initial surgery (21, 22). Adjuvant chemotherapy or radiation may improve the patient's prognosis, but there is insufficient confirmatory data.

Conclusion

Chronic thromboembolic pulmonary disease is one of the few potentially curable causes of pulmonary hypertension. With careful preoperative evaluation and postoperative care, an excellent long-term prognosis can be achieved in highly specialized centers. However, a broad differential remains important during the work-up. The alternative diagnosis of pulmonary artery sarcoma should be suggested for patients with no predisposing factors for embolism, inadequate relief of symptoms with anticoagulation, or with distinctly abnormal perfusion studies or CT scans.

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Elevated Homocysteine Levels in Patients with End-Stage Renal Disease

Ajith P. Nair, M.D.[1], Dmitry Nemirovsky, M.D. [2], Michael Kim, M.D. [2], Eliza B. Geer, M.D. [3], Michael E. Farkouh, M.D. [4], Jonathan Winston, M.D. [5], Jonathan L. Halperin, M.D. [2], and Michael J. Robbins, M.D.[2,6]

Abstract

Purpose: To examine the effect of hemodialysis on plasma homocysteine levels, and the relationship of these values to clinical cardiovascular events in patients with end-stage renal disease (ESRD).

Methods: Adults undergoing chronic hemodialysis were studied at baseline and at six months. Their clinical histories were obtained at the baseline visit, and measurements of plasma homocysteine concentration were made immediately prior to and following routine dialysis. The occurrence of clinical cardiovascular events was assessed over six months.

Results: We enrolled 147 patients (85 men and 62 women, age 58 ± 15 years) who required hemodialysis for 3.4 ± 3.4 years (mean ± SD). The median homocysteine level for this population (including both pre- and post-dialysis values) was 17.3 micromoles/L . Mean pre-dialysis plasma homocysteine levels of patients with clinical cardiovascular disease did not differ significantly from those without the disease (22.5 ± 9.9 vs. 25.4 ± 24.5 micromoles/L, respectively), nor did post-dialysis levels differ between these populations. During six months follow-up, rates of ischemic events were not related to hyperhomocysteinemia. The difference between mean pre- and post-dialysis homocysteine levels (26.3 ± 19.7 and 15.6 ± 11.4 micromoles/L, respectively) and the decline in homocysteine over the course of a single dialysis treatment session (10.3 ± 10.2 micromoles/L) were highly significant ($p<0.0005$).

Conclusions: Plasma homocysteine levels were elevated in 82% of 147 patients with ESRD and fell to the normal range in a majority of patients during a single dialysis treatment session. Mean pre-dialysis levels did not change significantly over six months, however, and plasma homocysteine levels did not predict cardiovascular events in this population. There was also a trend towards worse outcomes in patients with lower homocysteine levels, which correlates to findings from recent studies. Further studies are needed to clarify the association between hyperhomocysteinemia and coronary risk in patients with ESRD.

Key Words: Hemodialysis, homocysteine, cardiovascular disease, end-stage renal disease, hyperhomocysteinemia.

Introduction

THE PREVALENCE OF END-STAGE renal disease (ESRD) requiring dialysis is increasing. Approximately 40% of patients with this disorder have clinical manifestations of atherosclerotic cardiovascular disease, with an annual cardiovascular mortality rate approaching 10% (1). This mortality rate is 10- to 20-fold greater than for people with normal renal function (2–7). While traditional cardiovascular risk factors such as hypertension and dyslipidemia have been implicated (8), these alone are not sufficient to account for the increased mortality in this population. Hence nontraditional risk factors such as chronic inflammation and hyperhomocysteinemia have been investigated as potentially contributory.

Elevated plasma levels of homocysteine have been associated with adverse cardiovascular outcomes in patients with ESRD (9 – 17). In a study of 176 hemodialysis patients, the odds ratio for developing vascular complications was 2.9 for those with homocysteine concentrations over 27.8 micromoles/L compared to patients with low homocysteine levels, and B vitamin levels were reduced in those with complications (11). Both fatal and nonfatal coronary events occurred more frequently

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From [1]The Department of Internal Medicine, [2]The Zena and Michael A. Wiener Cardiovascular Institute, and Divisions of [3]Endocrinology and [5]Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; [4]Division of Cardiology, Department of Medicine, New York University, New York, NY; and [6]Department of Medicine, St. John's-Queens Hospital, New York, NY.

Address all correspondence to Michael J. Robbins, M.D., The Cardiovascular Institute, Box 1030, Mount Sinai Medical Center, One East 100th Street, New York, NY 10029-6574; e-mail: michael.robbins@mssm.edu

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in patients with homocysteine levels greater than 27 μM/L in a study of 73 maintenance dialysis patients (relative risk 3.0 and 4.4, respectively) (12). In other studies, the relative risk for cardiovascular events increased by 1% and mortality increased by 3% for each micromolar increase in homocysteine concentration (13, 16).

A number of variables influence plasma homocysteine concentration in patients undergoing dialysis, including the proportion of homocysteine bound to plasma proteins (80%), the dialysis membrane composition, and plasma folate and B_{12} levels (cofactors in homocysteine metabolism) (18, 19). To examine the influence of dialysis on plasma homocysteine levels and the relationship of these values to clinical cardiovascular disease, we systematically measured plasma homocysteine prior to and immediately following dialysis in a large population of patients with ESRD at two hospitals.

Methods

Adult patients with established ESRD undergoing maintenance hemodialysis at two hospital sites were studied at baseline and six months later. Eligibility and clinical characteristics were established by review of medical records. Inclusion criteria included ESRD requiring chronic maintenance hemodialysis, written informed consent according to a protocol approved by the institutional review board governing research involving human subjects, and the ability to give a baseline blood sample. Exclusion criteria included a history of acute coronary syndrome (including unstable angina pectoris or acute myocardial infarction) or coronary intervention within the preceding thirty days.

Blood was obtained for assay of total homocysteine concentration immediately prior to routine hemodialysis (before the administration of heparin), and again immediately after dialysis at baseline and after six months. Samples were centrifuged for 15 minutes at 3,000 rpm, and supernatant plasma was shipped frozen to a commercial laboratory (Quest Diagnostics, Inc.). Samples were processed by protein decoupling, reduction with tri-n-butylphosphine, and thiol-specific fluorogenic separation. Total plasma homocysteine (the aggregate of all homocysteinyl moieties, whether in the sulfhydryl or disulfide form, free or protein-bound) was measured by reversed-phase liquid chromatography with fluorescence detection, and expressed as micromoles/L (normal range = 0 – 15 micromoles/L). Maintenance hemodialysis was carried out across Fresenius F6, F8, or F80 polysulfone membranes.

A clinical history questionnaire, including risk factors for coronary artery disease (CAD) (tobacco use, elevated cholesterol, diabetes mellitus, hypertension and family history of CAD), number of years dialysis had been required, and manifestations of overt cardiovascular disease (angina, myocardial infarction, coronary revascularization) was completed at the baseline visit. Six months later, a follow-up questionnaire was completed documenting interval cardiac events, and pre- and post-dialysis homocysteine values were measured. Serum vitamin B_{12} (ng/L) and folate (ng/mL) levels were measured at one hospital site (normal ranges: 200 – 1100 ng/L for vitamin B_{12} and >3 ng/mL for folate).

Statistical Analysis

Associations between clinical history of cardiovascular disease and plasma homocysteine measurements were evaluated by linear regression and the Mann-Whitney U-test. The change in homocysteine levels during dialysis was analyzed using the Wilcoxon signed-rank test. To estimate the mean difference in plasma homocysteine across dialysis treatment sessions, we assumed that the differences were normally distributed, and estimated the mean of that difference by maximum likelihood estimation, censoring test values at the lower limit of detection. The relationships between folate, vitamin B_{12} and homocysteine were analyzed using interval regression. Statistical analysis was performed using Stata version 6.0. Results are reported as the mean ± standard deviation; statistical significance was accepted at the 0.05 level.

Results

Of the 152 stable adult patients identified as the screening cohort, four declined to participate and one subsequently underwent kidney transplantation. Table 1 displays the characteristics of the study population, which consisted of 85 men and 62 women, mean age 58 ± 15.3 years, who had required dialysis for 3.4 ± 3.4 years. Forty-five (45) patients (30%) had symptomatic coronary artery disease, which manifested as angina pectoris (20%), myocardial infarction (15%) or myocardial revascularization (13%). Fifty-five (55) patients (37%) had diabetes mellitus, and 64 patients (43%) had a history of tobacco use.

In Table 2, plasma homocysteine levels are compared for patients with and without clinical cardiovascular disease. Mean pre-dialysis plasma homocysteine levels in patients with prior angina pectoris, myocardial infarction (MI) or revascular-

TABLE 1
Clinical Characteristics of the Study Population

Characteristics	**Number of Patients (n = 147)**
Age (mean, min-max, years)	57.7 (21 – 86)
Male (percent)	58
Years on dialysis (mean, min-max)	3.4 (0.1 – 18)
History of myocardial infarction	22 (15%)
History of angina	30 (20%)
History of CABG or PTCA	19 (13%)
Family history of CAD	28 (19%)
Hypertension	118 (80%)
Diabetes mellitus	55 (37%)
Insulin dependent (percent of DM)	28 (51%)
Mean HbA1c (units)	7.8%
Smoking	
Within 1 month	29 (20%)
Ever	61 (43%)
Mean pack-years	19.1
Serum cholesterol (mg/dL)	167
Mean pre-dialysis systolic BP	155
Mean post-dialysis systolic BP	147
Mean pre-dialysis diastolic BP	82
Mean post-dialysis diastolic BP	78

CABG = coronary artery bypass graft
PTA = percutaneous transluminal coronary angioplasty
CAD = coronary artery disease
DM = diabetes mellitus
BP = blood pressure

ization did not differ significantly from levels in those without such history (22.5 ± 9.9 micromoles/L vs. 25.4 ± 24.5 micromoles/L, p=NS), nor did post-dialysis levels differ significantly between these populations. Homocysteine levels did not differ between patients on the basis of risk factors for coronary disease. During six-month follow-up, rates of ischemic events were not significantly associated with homocysteine values, although there was a trend towards higher event rates being associated with lower homocysteine values.

Table 3 shows pre- and post-dialysis homocysteine levels, categorized as normal (0 – 15 micromoles/L), mildly elevated (15 – 30 micromoles/L), intermediately elevated (30 – 100 micromoles/L), and markedly elevated (> 100 micromoles/L). The median homocysteine level for this population (including both pre- and post-dialysis values) was 17.3 micromoles/L. Of the 147 patients, 121 (82%) had elevated (>15 micromoles/L) homocysteine levels prior to dialysis. In contrast, homocysteine levels immediately after dialysis were elevated in only 58 patients (40%). Of the 106 patients with pre-dialysis levels above the median, 67 (63%) fell below the median after dialysis, while all but one (98%) of 41 patients with low pre-dialysis homocysteine levels

TABLE 2
Homocysteine Levels in Patients in Relation to Clinical Cardiovascular Disease

	Number	**Mean pre-HD homocysteine levels**	**Number**	**Mean post-HD homocysteine levels**
Angina, MI, CABG, PTCA	No (101)	25.4 ± 24.5	No (101)	14.6 ± 16.8
(history of at baseline)	Yes (45)	22.5 ± 9.9 (p=0.11)	Yes (45)	13.3 ± 5.3 (p=0.30)
Angina, MI, CVA, PTCA, CABG, PVD	No (134)	25.4 ± 19.4	No (134)	15.0 ± 11.2
procedure (at six months)	Yes (16)	19.1 ± 8.5 (p=0.04)	Yes (16)	11.6 ± 6.0 (p=0.14)
DM	No (91)	26.7 ± 22.0	No (91)	14.1 ± 17.4
	Yes (55)	20.9 ± 19.1 (p=0.25)	Yes (55)	14.5 ± 6.7 (p=0.66)
HTN	No (29)	20.1 ± 25.2	No (29)	13.5 ± 7.7
	Yes (117)	25.7 ± 19.3 (p=0.65)	Yes (117)	14.4 ± 15.5(p=0.28)
Cholesterol >240	No (137)	25.3 ± 18.7	No (136)	15.0 ± 11.0
	Yes (8)	26.1 ± 14.8 (p=0.96)	Yes (8)	15.3 ± 6.4 (p=0.71)
Smoking within one month	No (118)	25.7 ± 20.3	No (117)	15.2 ± 11.5
	Yes (29)	23.3 ± 7.8 (p=0.83)	Yes (29)	13.7 ± 7.4 (p=0.32)

MI =myocardial infarction
CABG = coronary artery bypass graft
PTCA = percutaneous transluminal coronary angioplasty
CVA = cerebral vascular accident
PVD = peripheral vascular disease
DM = diabetes mellitus
HTN = hypertension

remained below the median value after dialysis. The difference between mean homocysteine levels before and after dialysis (26.3 ± 19.7 and 15.6 ± 11.4 micromoles/L, respectively) and the mean decline in homocysteine over the course of a single dialysis treatment session, 10.3 ± 10.2 micromoles/L, was highly significant ($p<0.0005$).

Baseline and six-month pre-dialysis homocysteine values are compared in Table 4. Pre-dialysis homocysteine values did not decrease over this period. Table 5 shows pre-dialysis serum vitamin B_{12} and folate values in a subgroup of 62 patients at six months. Fifty-five (55) of these 62 patients (89%) had normal vitamin B_{12} levels, while 3 (5%) had values below normal and 4 (6%) had values above normal. All 62 patients had normal serum folate values. According to interval regression analysis, there was a significant inverse relationship between folate and homocysteine levels, but no relationship between vitamin B_{12} and homocysteine levels.

Discussion

A sulfur-containing amino acid derived from dietary methionine, homocysteine is metabolized along two pathways. Remethylation to methionine is catalyzed by methionine synthase, which requires vitamin B_{12} as a co-factor. Folate, converted to 5-methyltetrahydrofolate, serves as the methyl donor in this reaction. In the presence of excess methionine, the trans-sulfuration pathway converts homocysteine to cysteine via a vitamin B_6-dependent enzyme (20). Normal levels of plasma homocysteine fall between 5 and 15 micromoles/L. Elevations can result from genetic defects in the enzymes involved in homocysteine metabolism, deficiencies in the vitamins that serve as metabolic cofactors, or a number of disease states. Deficiency of cystathionine β-synthase results in homocysteinuria, in which plasma homocysteine levels rise to 100–400 micromoles/L. Though homocysteinuria occurs in only 1 of 100,000 births, about half the patients with this disease develop atherothrombotic complications by age 30.

A much more common genetic cause of hyperhomocysteinemia is a point mutation in the gene for methylene tetrahydrofolate reductase (MTHFR), an enzyme critical to the remethylation cycle (21). This mutation, also referred to as the TT polymorphism or the thermolabile variant, re-

TABLE 3

Homocysteine Levels before and after Hemodialysis (micromoles/L)

	Pre-dialysis	Post-dialysis			
		<15	*15–30*	*30–100*	*>100*
Normal (<15)	26	25	1	0	0
Moderate elevation (15–30)	85	58	26	1	0
Intermediate elevation (30–100)	35	6	28	1	0
Severe elevation (>100)	1	0	0	0	1

TABLE 4

Homocysteine Levels over Six Months (n=123)

	Pre-HD homocysteine	Post-HD homocysteine	Min-max
Month 0	26.3 ± 19.7	15.6 ± 11.4	0–211
Month 6	26.2 ± 9.4	N/A	10.1–56.3

HD = hemodialysis

TABLE 5

Baseline Pre-dialysis Serum Vitamin B_{12} and Folate Levels (n = 62)

B12 (ng/L)	Low (<200)	Normal (200–1100)	High (>1100)
Number of patients	3	55	4
Folate (ng/mL)	Low (0–2.1)	Borderline (2.2–3)	Normal (>3)
Number of patients	0	0	62

sults from a C-to-T substitution in base 677, which causes an amino acid change of alanine to valine. The homozygous state of this mutation occurs in 10–15% of the Caucasian population and is associated with a 25–50% increase in plasma homocysteine levels, amplified by folate deficiency (21–24). Heterozygotes do not appear to share the incremental risk for developing hyperhomocysteinemia. A meta-analysis of 40 European studies encompassing 11,162 patients homozygous for the TT polymorphism and 12,758 matched controls found a 16% increase in risk of clinical CAD among individuals with the defect (23). The observation was not sustained in North American studies conducted after fortification of the dietary sources with B vitamins and folic acid became commonplace.

Hyperhomocysteinemia also results from deficiencies in folic acid, vitamin B_{12} and, to a lesser extent, pyridoxine (vitamin B_6); two thirds of patients with elevated homocysteine levels have low plasma levels of these vitamins or related co-enzymes (25). In patients with normal renal function, a single 400–600 μg dose of folic acid produces a 20–30% decrease in plasma homocysteine levels (26).

Up to 7% of the general population and almost 50% of patients with clinical atherosclerosis have moderate plasma homocysteine elevations (27). And hyperhomocysteinemia has been identified in 85% of patients undergoing maintenance dialysis in previous studies (28). In addition to atherosclerosis and renal dysfunction, hyperhomocysteinemia has been associated with certain malignancies and with cigarette smoking in patients treated with drugs that interfere with folate metabolism.

In 1996 the U.S. Food and Drug Administration, motivated by evidence that folic acid supplementation reduced the incidence of congenital neural tube defects, issued a regulation requiring enriched grain products to be fortified with folic acid at a concentration sufficient to increase the average daily intake by 100 μg per individual. By January 1998 the regulation had been fully implemented. Based on one trial, the proportion of the population with homocysteine levels greater than 13 micromoles/L decreased during this period from 18.7 to 9.8% (29).

In addition to coronary artery disease, hyperhomocysteinemia has been linked with peripheral vascular and cerebrovascular disease, venous thrombosis, osteoporotic fractures and Alzheimer's disease. Proposed mechanisms for the role of homocysteine in the development or progression of vascular disease include endothelial dysfunction related to oxidative damage, oxidation of low-density lipoprotein (LDL)-cholesterol, smooth muscle cell proliferation and abnormalities of coagulation (30–38). Homocysteine is auto-oxidized in plasma to mixed disulfides, thiolactone and the reactive oxygen species, superoxide and hydrogen peroxide (30), which have been directly linked to endothelial injury (31). The thiolactone metabolite enhances uptake of LDL-cholesterol by macrophages critical to the instability of the atherosclerotic plaque (30, 34, 35).

Exposure of endothelial cells to homocysteine for prolonged periods inhibits the function of nitric oxide synthase, impairing the vasodilatory and antithrombotic effects of nitric oxide (36). And several studies have shown improvement in arterial endothelial function following homocysteine-lowering therapy (39–41). Homocysteine has been shown to upregulate monocyte chemoattractant protein-1 and interleukin-8 and to stimulate smooth muscle cell proliferation leading to atheroma formation (42–44).

Finally, homocysteine has several prothrombotic effects, including activation of factors VIIa and V, and inhibition of protein C, thrombomodulin and endogenous heparin sulfate (45–48). Homocysteine induces tissue factor expression and reduces the binding of tissue plasminogen activator to its receptor on the endothelial cell (30). All of these effects lead to the generation of thrombin and have been invoked to explain the association of hyperhomocysteinemia with venous thrombosis.

Of the patients with ESRD we studied, 82% had elevated plasma homocysteine levels (≥ 15 micromoles/L) at baseline. In 63% of those with homocysteine levels above the median (17.3 micromoles/L), levels fell to below the median after a single hemodialysis session, such that only 39% had persistent elevations. The fall in homocysteine levels after a single dialysis treatment is consistent with other studies and consistent with the additional observation that initial homocysteine levels were not significantly different from those measured after six months of dialysis. Since these patients were undergoing dialysis regularly before enrollment, any change in homocysteine levels may already have occurred and may not have been detected over the course of the study.

We were unable to demonstrate a relationship between plasma homocysteine and either a history of CAD or its development over a six-month period of observation. On the contrary, there was a slightly higher prevalence of CAD among those with lower homocysteine levels. The mean homocysteine level of those suffering ischemic events during follow-up was 19.1 ± 8.5 micromoles/L, compared with 25 ± 19.4 micromoles/L among those who remained event free (p=0.04). There was no correlation between homocysteine levels and cardiovascular events in our patient population; in fact, a slight inverse correlation between homocysteine levels and outcome was suggested.

Plasma homocysteine levels rise with increasing renal dysfunction (18, 19, 49). Furthermore, dialysis transiently reduces homocysteine levels for roughly eight hours, after which they rise again (50). It has also been shown that plasma homocysteine levels rise in living kidney donors immediately after uninephrectomy and progressively decline as renal function improves (51). The mechanism of these elevated homocysteine levels is not clear, however, since renal homocysteine excretion accounts for less than 1% of its elimination. The amount of homocysteine removed by dialysis did not contribute significantly to the fall in homocysteine levels in animals, and although folate-dependent transmethylation and remethylation pathways seem diminished in patients undergoing dialysis compared to normal controls (52), defects in transsulfuration pathways may contribute to homocysteinemia in patients with ESRD (53).

Multiple, retrospective, observational studies of adult populations have suggested that even mild elevations in homocysteine levels may confer an increased risk for cardiovascular disease and that hyperhomocysteinemia is associated with more recurrent events and greater mortality for those with already-established vascular disease (54–59). However, the results of large, prospective studies have been inconsistent. In a cohort of 14,000 male physicians without known atherosclerosis enrolled in the Physicians' Health Study, elevated homocysteine levels at entry were associated with a threefold increased risk of MI after five years, but the finding was no longer statistically significant at 7.5 years. Similar prospective, observational data from the MRFIT study showed no relationship between baseline homocysteine level and subsequent risk of MI or cardiac mortality (60).

In the absence of randomized trials examining homocysteine-lowering strategies for primary and secondary prevention, it remains uncertain whether the relationship between hyperhomocysteinemia and coronary disease is causal. In a randomized trial of folic acid (5 mg/day) in 593 patients with stable CAD on statin therapy, plasma homocysteine levels declined by 18% yet, at four-year follow-up, there was no difference in vascular events or all-cause mortality (61). In the Vitamin Intervention for Stroke Prevention (VISP) trial, 3,680 patients with a history of stroke were randomized to low-dose (20 μg) folic acid, with 200 μg vitamin B_6 and 6 μg vitamin B_{12} daily or high-dose (2.5 mg) folic acid, 25 mg vitamin B_6 and 0.4 mg vitamin B_{12}) (62). Although there was a correlation between baseline homocysteine levels and recurrent stroke, coronary events and death at two years, there was no difference between the two homocysteine-lowering regimens on those endpoints. In the Swiss Heart Study, 553 patients undergoing percutaneous coronary intervention (PCI) were randomized to 6 months of homocysteine-lowering therapy (folic acid, vitamin B_{12} and vitamin B_6) or placebo (63). At one year of follow-up, there was a 68% relative risk reduction in the composite endpoint of death, MI and tricuspid valve replacement (TVR) with homocysteine-lowering therapy. Subsequently, however, the Dutch FACIT study found that coronary restenosis at six months occurred significantly more frequently among 636 patients receiving intravenous and then oral homocysteine-lowering therapy following elective coronary stenting compared to those given placebo (64), despite reduction of homocysteine levels from 12.2 micromoles/L to 9.0 micromoles/L in the therapy group and no change in the placebo group. Other studies addressing this issue are currently in progress.

In the ESRD population, deficiencies of vitamins B_6, B_{12} and folic acid are rare, even when plasma homocysteine levels are elevated (11), suggesting a defect in metabolism. Although the patients in our study had normal serum folate levels (>3 ng/mL), elevated homocysteine levels were still associated with lower folate values, consistent with findings in other studies that elevated folate levels are an independent predictor of plasma homocysteine levels in patients undergoing dialysis (64). These observations suggest that patients with ESRD may require greater folic acid supplementation than conventionally prescribed, or that supplemental administration of vitamin B_{12} and B_6 might lower homocysteine levels in this setting (65–68).

The results of our study are similar to others that have shown a paradoxically inverse correlation of plasma homocysteine levels and cardiovascular mortality in patients undergoing dialysis. Suliman et al., found lower homocysteine levels in patients with established coronary disease associated with worse survival rates (69). In another study of 367 patients on maintenance hemodialysis, those with homocysteine levels in the lowest quartile had higher mortality rates than those with higher homocysteine levels. Several studies have demonstrated that homocysteine levels are related to serum albumin concentration, suggesting that homocysteine may be a marker of nutritional status and that impaired nutrition may be related to adverse coronary outcomes in patients with ESRD (49). The "malnutrition, inflammation and atherosclerosis complex syndrome" may thus describe the process of inflammation in patients with chronic renal insufficiency who are wasted and succumb to cardiovascular events (70). In this scenario, malnutrition and chronic inflammation may confound the association of homocysteine with cardiovascular events, a "reverse epidemiology" of risk factors that complicates assessment of homocysteine levels and other indicators of cardiovascular risk, as occurs in patients with advanced congestive heart failure (71–75). Thus, while homocysteine may be a marker of atherosclerosis in patients without renal dysfunction, levels in patients maintained on dialysis cannot be fully interpreted without recognition of their nutritional status and concurrent inflammatory processes that may be related to overall mortality.

Summary

Despite previous studies showing that homocysteine is a predictor of coronary outcomes in dialysis patients, our findings fail to support such a correlation. Hyperhomocysteinemia was not predictive of adverse cardiac outcome in the population we studied, and there was a trend towards worse outcomes with lower homocysteine levels. While homocysteine levels may partially account for thrombotic disease in dialysis patients, the correlation is confounded by malnutrition and inflammation. This study involved a relatively short period of follow-up, and additional studies involving a larger sample size and longer follow-up are needed to assess the impact of homocysteine in patients with ESRD. Such studies should take into account markers of inflammation and malnutrition that may contribute to increased cardiovascular morbidity.

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Mean Frequency of Premature Ventricular Complexes As Predictor of Malignant Ventricular Arrhythmias

Zia I. Carrim, M.B. Ch.B., and Ashraf A. Khan, B.Med.Sci.

Abstract

Aim: The aim was to test the hypothesis that mean frequency of premature ventricular complexes (PVCs) correlates with vulnerability to malignant arrhythmias such as ventricular tachycardia and/or ventricular fibrillation (VT/VF).

Methods: Patients with an implantable cardioverter defibrillator (ICD) device for underlying ischemic or non-ischemic cardiac pathology were selected from a database. Availability of total count of single (s) PVCs and runs (r) of PVCs was the only inclusion criterion. Forty-four subjects (6 females and 38 males) aged 18–74 years (mean 57.1 years), were eligible. All had a European Pacemaker Identification Card (EPIC) documenting left ventricular ejection fraction (LVEF). The frequency of recorded episodes of VT and VF was obtained from ICD memory.

Results: Among patients with ischemic heart disease (IHD) and those with IHD and an LVEF of less than 30%, the mean frequency of PVCs was significantly higher in those with subsequent episodes of VT/VF compared to those without subsequent episodes ($p < 0.05$ for sPVCs and rPVCs in both groups).

Conclusion: Among patients with IHD, mean frequency of PVCs is a useful marker of vulnerability to potentially fatal arrhythmias and may be a useful tool for the risk stratification of patients.

Key Words: Premature ventricular complexes, ventricular tachycardia, ventricular fibrillation, implantable cardioverter defibrillator.

Introduction

RE-ENTRY IN DAMAGED VENTRICULAR MUSCLE, automaticity in the His-Purkinje fibers, and triggered activity due to afterdepolarizations have been found to be the main mechanisms responsible for ventricular arrhythmias (1–3). Clinical and epidemiological associations between premature ventricular complexes (PVCs) and potentially fatal ventricular arrhythmias have been recognized for several years; much of the initial research was done by Lown and his colleagues in the 1970s (4–8). In the setting of the coronary care unit, he observed that PVCs invariably precede ventricular fibrillation (VF) and that suppression of PVCs reduces the incidence of VF (7). It is also known that almost 90% of patients with ischemic heart disease (IHD) exhibit ectopic activity. The mere presence of ectopic activity cannot, therefore, be a prognostic marker of risk (4, 9, 10). Using Holter monitoring, Lown proposed a grading system for PVCs based on frequency, persistence, multiformity, repetitive pattern and degree of prematurity (5, 10). Only complex PVCs (R-on-T, runs of two or more, multiform or bigeminal) were found to impart an increased risk of sudden cardiac death (10, 11).

The development of third-generation implantable cardioverter defibrillator (ICD) technology, with enhanced storage capacity, has led to important advances in the understanding and treatment of potentially fatal arrhythmias. Studies of stored intracardiac electrograms (EGMs) from ICD devices have examined heart rate variability (HRV) and PVCs as predictors of arrhythmic events (1, 2, 12–14). The main purpose of our study was to examine the possibility of a relationship between mean frequency of PVCs and a predisposition to malignant ventricular arrhythmias in a group of patients who had received ICD devices for underlying structural, ischemic or electrophysiological cardiac pathology.

Methods

Forty-four subjects, selected from a database of 104 ICD patients, were included in this study. Of these, 6 were females aged 18–61 years (mean 47.9 years) and 38 were males aged 25–74 years (mean 58.9 years). Availability of total count of single PVCs

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College of Medicine, University of Edinburgh, Scotland, United Kingdom.

Address all correspondence to Zia I. Carrim M.B., Ch.B. (Hons.), Flat 3, 19 High Riggs, Edinburgh, EH3 9BW, Scotland, United Kingdom; email: zia.carrim@doctors.org.uk

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Glossary

CAST = Cardiac Arrhythmia Suppression Trial
EGM = electrogram
EPIC = European Pacemaker Identification Card
EPS = electrophysiological studies
EURID = European Registry for Implantable Defibrillators
HRV = heart rate variability
IAPM = International Association of Prosthesis Manufacturers
ICD = implantable cardioverter defibrillator
IHD = ischemic heart disease
LVEF = left ventricular ejection fraction
MADIT = Multicenter Automatic Defibrillator Implantation Trial
MUSTT = Multicenter Unsustained Tachycardia Trial
PVC = premature ventricular complex
rPVC = runs of PVCs
sPVC = single PVC
VF = ventricular fibrillation
VT = ventricular tachycardia
VT/VF = VT and/or VF

(sPVC) and runs of PVCs (rPVC) was the only inclusion criterion. All subjects who satisfied the criterion had ICD devices of the GEM series (Medtronic Inc, Minneapolis, MN). This was actually coincidental, since the patients' choice of device had been independent of underlying pathology. The time interval over which PVC counts were registered in each patient varied between 21 and 1,073 days (mean 421 days). All patients in our series had European Pacemaker Identification Cards (EPIC) (IAPM/EURID, 1999).

Notes for each of the 44 subjects were reviewed. The total number of episodes of VT or VF and counts of PVCs over a defined period of time following implantation were obtained from records of the last interrogation of the ICD device. Left ventricular ejection fraction (LVEF), underlying pathology, main symptom, previous anti-arrhythmic treatment and device model were obtained from the EPIC. A correction to the total number of recorded episodes of VT and/or VF (VT/VF) was applied by subtracting the number of induced episodes of VT or VF during implantation. Mean frequency of PVCs was calculated for each patient and recorded in cycles per hour (cyc/hr).

Statistical analysis of data was performed using Minitab software (Minitab Inc, State College, PA). The Mann-Whitney test was used for non-parametric data and the χ^2 test was used for categorical data. A value of $p<0.05$ was deemed significant.

Results

The table shows characteristics of the study population. Subjects with ischemic heart disease comprised the single largest group in terms of underlying pathology (at least 43% of the total) and at least 39% of the subjects had an LVEF of less than 30%. Cardiac arrest and syncope were the main modes of presentation in 82% of our study population. Twenty-two patients (50%) had received anti-arrhythmic medication, mainly amiodarone, before being considered for an ICD. Twenty-one subjects (48%) had had at least one episode of VT/VF, 6 (13.5%) had had at least one episode of VT only and 3 (6.8%) had had at least one episode of VF only. The frequency of sPVCs in the overall population ranged from

TABLE
Characteristics of the Study Population and Its Subgroups

Characteristic	No of subjects (%)		
	Overall	IHD	IHD & LVEF < 30%
Underlying pathology			
Ischemic heart disease	19 (43.2)	-	-
Cardiomyopathy	4 (9.1)	-	-
Other (valvular heart disease, long QT syndrome)	2 (4.5)	-	-
Unknown	19 (43.2)	-	-
Left ventricular ejection fraction (%)			
< 30	17 (38.6)	11 (57.9)	-
30–50	13 (29.5)	5 (26.3)	-
> 50	8 (18.2)	1 (5.3)	-
Unknown	6 (13.6)	2 (10.5)	-
Main Symptom			
Syncope	15 (34.1)	4 (21.1)	3 (27.3)
Dizzy spells	2 (4.5)	0 (0.0)	0 (0.0)
Cardiac arrest	21 (47.7)	13 (68.4)	7 (63.6)
Palpitation	3 (6.8)	2 (10.5)	1 (9.1)
Other	3 (6.8)	0 (0.0)	0 (0.0)
Episodes			
At least one episode of VT and/or VF	21 (47.7)	9 (47.4)	6 (54.5)
At least one episode of VT only	6 (13.5)	0 (0.0)	0 (0.0)
At least one episode of VF only	3 (6.8)	2 (10.5)	2 (18.2)
Medication			
Amiodarone only	12 (27.3)	6 (31.6)	3 (27.3)
Amiodarone + other antiarrhythmic	5 (11.4)	4 (21.1)	2 (18.2)
Other anti-arrhythmic	5 (11.4)	1 (5.3)	1 (9.1)
None	10 (22.7)	3 (15.8)	2 (18.2)

IHD = ischemic heart disease, VT = ventricular tachycardia, VF = ventricular fibrillation.

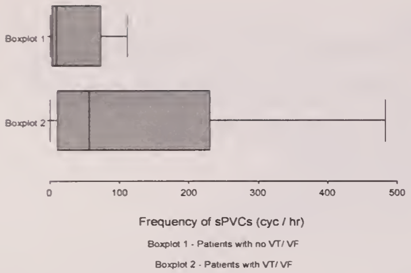


Fig. 1. Boxplots showing distribution of frequency of sPVCs in overall population.
sPVC = single premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

0.1 – 791 cyc/hr (mean 103 cyc/hr), while the frequency of rPVCs ranged from 0 – 1,473 cyc/hr (mean 45.7 cyc/hr). The frequency of sPVCs was greater than that of rPVCs in all but 2 patients. As shown in Fig. 1, there was no statistically significant difference between the frequency of sPVCs in patients with VT/VF subsequent to implant compared to the frequency in patients with no VT/VF (p=0.078). A similar result was obtained for the frequency of rPVCs, where the Mann-Whitney test revealed p=0.15 (Fig. 2). There was no significant association between degree of impairment of left ventricular function and mean frequency of sPVCs and rPVCs (p=0.747 and p=0.463, respectively). Chi-squared test showed no significant association between LVEF, dichotomized at 30%, and presence or absence of VT/VF.

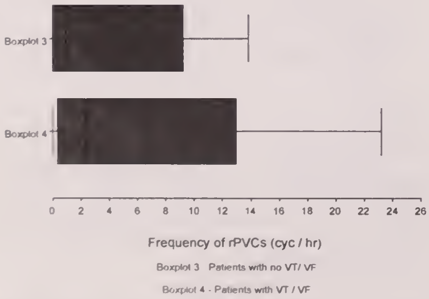


Fig. 2. Boxplots showing distribution of frequency of rPVCs in overall population
rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

In the population subgroup having IHD as the underlying pathology, 18 subjects were male and 1 was female. The age range was 44 – 74 years (mean 62 years) and 11 subjects (57.9%) had an LVEF of less than 30 %. Cardiac arrest and syncope were the main modes of presentation in nearly 90% of the patients (Table). The frequency of sPVCs in this subgroup ranged from 0.1 – 398 cyc/hr, while that of rPVCs ranged from 0.0041 – 237 cyc/hr. In contrast to the overall population, the frequency of sPVCs (Fig. 3) in the IHD subgroup was significantly lower in those with no VT/VF compared to those with VT/VF (p=0.0305). The frequency of rPVCs in the IHD subgroup, although having a lower predictive value (p=0.0373) compared to sPVCs, was also significantly lower in those with no VT/VF compared to those with VT/VF (Fig. 4). There was no significant association between degree of left ventricular impairment and mean frequency of sPVCs or rPVCs (p=0.514 and p=0.802, respectively).

Among the 11 patients with an LVEF of less than 30% and IHD as underlying pathology, the frequency of sPVCs ranged from 0.37 – 281 cyc/hr and that of rPVCs ranged from 0.0041 – 13 cyc/hr. Six patients had at least one episode of VT/VF (Table). The frequency of sPVCs and that of rPVCs within this subset were significantly lower in patients with no VT/VF compared to those with documented VT/VF (p=0.0225 in both cases). Fig. 5 summarizes the main findings.

Discussion

The progression of ventricular tachycardia (VT) to ventricular fibrillation (VF) and then to asystole is the most common sequence of events involved in fatal arrhythmias (15). While conventional risk factors such as

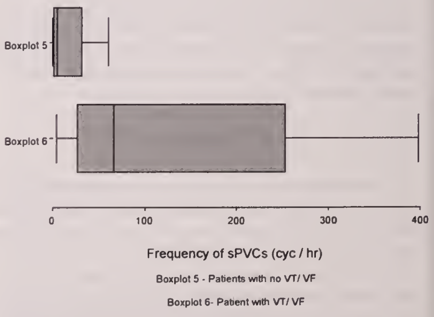


Fig. 3. Boxplots showing distribution of frequency of sPVCs in patients with IHD.
sPVC = single premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.

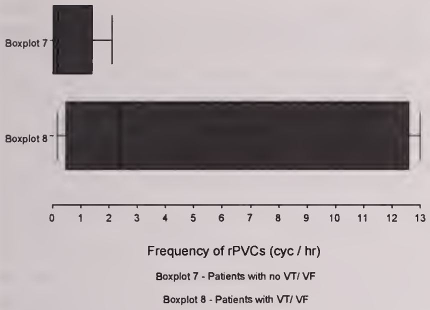
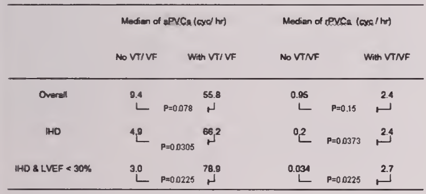


Fig. 4. Boxplots showing distribution of frequency of rPVCs in patients with IHD.
rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation.



	Median of sPVCs (cyc/ hr)			Median of rPVCs (cyc / hr)		
	No VT/ VF		With VT/ VF	No VT/VF		With VT/VF
Overall	9.4	P=0.078	55.8	0.95	P=0.15	2.4
IHD	4.9	P=0.0305	66.2	0.2	P=0.0373	2.4
IHD & LVEF < 30%	3.0	P=0.0225	78.9	0.034	P=0.0225	2.7

Fig. 5. Summary of predictive values of sPVCs and rPVCs as shown by the Mann-Whitney Test.
sPVC = single premature ventricular complex, rPVC = run of premature ventricular complex, VT/VF = ventricular tachycardia and/or ventricular fibrillation, IHD = ischemic heart disease, LVEF = left ventricular ejection fraction.

diabetes, smoking, hypertension and hyperlipidemia are invaluable in identifying high-risk subgroups, they have little predictive value in terms of the risk of a fatal arrhythmic event (16). Markers such as non-sustained VT, late potentials on signal-averaged ECG, T wave alternans, heart rate variability, baroreflex sensitivity, width of the QRS complex and QT dispersion have also been studied as indicators of an increased risk of death from arrhythmias and have been shown to have variable predictive power (15, 17–27).

A low left ventricular ejection fraction, caused by poor myocardial contraction, continuing ischemia or left ventricular dilatation, is a powerful predictor of the risk of death (15, 16, 28–31). However, the clinical use of LVEF as a specific marker of the risk of death due to arrhythmias has limitations. As LVEF decreases, both total mortality and the absolute number of sudden deaths increase, but the proportion of total deaths due to cardiac arrhythmias decreases (15, 32–34). Most randomized trials comparing antiarrhythmics to ICD therapy have included the measurement of LVEF in combination with other predictors for arrhythmia (35–37). In the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT), patients underwent invasive electrophysiological studies (EPS) to determine inducibility of sustained tachyarrhythmias by programmed electrical stimulation (35, 37). In contrast, MADIT II and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) enrolled patients who had severely compromised LVEF (<36% and <30%, respectively) and no prior electrophysiological testing (38, 39). Both trials showed a significant reduction in mortality associated with the use of ICD therapy for primary prevention (38, 39).

Initially, it was thought that ambient forms of PVCs play a causal role in the genesis of malignant arrhythmias, and that the time and mode of the fatal event was fortuitous (31, 40, 41). This concept was fundamental to the early electrogenic theory for VF (41). However, with the development of a base of experimental information, the importance of structural and functional elements as major contributors to the pathophysiological evolution of fatal arrhythmias has been increasingly accepted. In the modified electrogenic theory, the interaction between structure and function is thought to convert pathophysiologically innocuous PVCs into triggering events for malignant arrhythmias (31, 41). Thus, the predictive value of PVCs in terms of risk of malignant arrhythmias depends on several conditioning factors, such as myocardial infarction, ventricular hypertrophy and cardiomyopathy (15, 41).

In our study population, which consisted of patients from several subgroups of structural and functional classification, there was no statistically significant difference between mean frequency of PVCs in patients with no VT/VF and those with VT/VF. However, in the IHD subgroup, where structural pathology was controlled, the difference between mean frequency of PVCs in those with VT/VF compared to those without VT/VF was statistically significant. This predictive power of mean frequency of PVCs was stronger for patients with IHD and an LVEF of less than 30%. We infer from these observations that the value of mean frequency of PVCs as a marker of risk of malignant arrhythmias is dependent on underlying structural factors. This is consistent with the modified electrogenic theory (41).

Several studies have assessed the significance of PVCs among patients with previous myocardial infarction and left ventricular failure. While some trials have suggested that higher frequencies of PVCs are associated with increased risk of sudden death (21, 30, 42–44), others have suggested that they are of little independent prognostic significance (17). Assessing the relationship between mean frequency of PVCs and mortality was beyond the scope and methodology of this study. However, our findings suggest that the mean frequency of PVCs may be a useful measure for the risk stratification of ICD patients known to have either IHD only or IHD and an LVEF of less than 30%. As shown in Fig. 5, patients with no documented episodes of VT/VF in the "IHD only" and "IHD and LVEF < 30%" subgroups have significantly lower mean frequencies of sPVCs and rPVCs. Therefore, identifying low-risk patients from this subgroup, based on a mean frequency of PVCs less than the median, is likely to have a very high specificity with potential implications for therapy-oriented decision making. Moreover, as suggested by a recent study showing a statistically significant increase in the frequency of atrial ectopics over the hour preceding atrial fibrillation, we postulate that changes in the frequency of PVCs may be useful indicators of transient destabilization capable of progressing to malignant arrhythmias (45).

Since the involvement of PVCs in the genesis of malignant arrhythmias is supported by experimental evidence, it was hypothesized that their suppression could result in improved survival. However, large-scale studies like the Cardiac Arrhythmia Suppression Trial (CAST) have disproved this (46, 47). In the CAST study, although suppression of ventricular arrhythmias was achieved with flecainide, encainide and moricizine, there was no improvement in long-term survival (46). It was postulated that induction of early afterdepolarizations could have increased triggered activity. This paradoxical observation has prompted many to also consider PVCs as a marker of the degree of cardiac impairment (2, 33). In our study, no direct, significant association was found between mean frequency of PVCs and degree of left ventricular impairment in the overall population or in the IHD subgroup. Furthermore, our data did not show LVEF, dichotomized at 30%, to be a determinant of arrhythmia recurrence (42). Although these findings contradict previous reports, it is also likely that our study was not adequately powered with respect to these observations.

While this study did not specifically examine the electrophysiological characteristics of PVCs and their relationships with ventricular arrhythmias, some observations can be made. Among patients with IHD, re-entry of the sinus beat due to temporary impairment of conductivity or excitability in ventricular muscle is thought to be the main mechanism responsible for the initiation of ventricular arrhythmias (1–3, 14, 48). Previous studies of EGMs in patients with IHD have shown that single PVCs are most commonly involved in the onset of ventricular arrhythmias (1, 3, 14). This observation is a possible explanation for the relatively higher predictive power of sPVCs compared to rPVCs, as illustrated in Figs. 3 and 4. However, we are unable to explain the consistently higher frequency of sPVCs compared to rPVCs observed in all but 2 of our patients.

There were several limitations to our study: (a) the overall study population was small, leading to an even smaller subgroup of patients with IHD; (b) the classification of patients into the IHD group was based on symptomatic presentation only, implying that some of the non-IHD patients with subclinical IHD may have been missed; (c) there was substantial variation in the number of days over which frequency of PVCs was calculated; (d) although our findings in relation to patients with IHD are statistically significant, we have been unable to characterize other trends, particularly in relation to LVEF; (e) the absence of categorical data, as is the case for underlying pathology in our overall population, implies that our figures are at best estimates; and (f) by examining only patients with an ICD, we excluded patients who are at risk of VT/VF but who did not receive ICDs. The correlation of PVCs with VT/VF in the latter group is likely to be very different.

Conclusion

The main finding of our study suggests that mean frequency of PVCs is a potentially useful marker of vulnerability to malignant arrhythmias in patients with IHD as underlying pathology. Elevated risk for sudden cardiac death clearly exists in clinical situations of left ventricular dysfunction, and has been extensively described. However, further risk stratification is needed. The challenge for clinicians is to identify those patients at the highest risk—individuals who would benefit from more extensive evaluation and more aggressive treatment.

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Successful Treatment of Cervical Spinal Epidural Abscess by Combined Hyperbaric Oxygenation

Kiyotaka Kohshi, M.D.[1], Haruhiko Abe, M.D.[2], Yoshito Mizoguchi, M.D.[3], and Masayuki Shimokobe, M.D.[4]

Abstract

A 49-year-old man underwent hyperbaric oxygen (HBO) therapy for the treatment of primary spinal epidural abscess. Although the epidural abscess was initially treated with antibiotic (cefozopran) for 5 days, he subsequently developed motor weakness, paresthesia and urinary retention. MRI demonstrated spinal cord compression at the C1–C4 level. HBO therapy was added to the antibiotic regimen, and 3 days later we found clinical evidence of a response to treatment. Neurological symptoms were relieved 13 days after HBO therapy. This case suggests that HBO therapy is an effective therapeutic adjunct for the treatment of spinal epidural abscess.

Key Words: Spinal epidural abscess, hyperbaric oxygen, infection.

Introduction

Spinal epidural abscess is an uncommon but potentially serious condition that requires urgent treatment. The standard treatment for this condition is antibiotic therapy with surgical decompression or drainage. Although early diagnosis with improved imaging techniques, prompt surgical intervention and effective antibiotic development has decreased mortality, the mortality rate remains fairly high even in recent series (1–3). Recently, the incidence of this disease has increased in relation to increased age, underlying diseases, intravenous drug abuse, and spinal procedures (4, 5). Hyperbaric oxygen (HBO) therapy has been used to treat a variety of infected, hypoperfused, and hypoxic wounds. It is helpful because the phagocytosis of leukocytes is substantially impaired at the low oxygen tensions often observed in wounds (6–10). In addition, oxygen may enhance a direct bactericidal or bacteriostatic effect of antibiotics (6, 11). Now HBO therapy has an important role in the treatment of many patients with anaerobic and aerobic bacterial infections (6). We present a case in which cervical epidural abscess was successfully managed conservatively with antibiotic treatment combined with HBO therapy.

Case Report

A 49-year-old laborer without diabetes mellitus or other systemic diseases complained of left neck pain. He had fallen from a precipice approximately 12 meters high, onto tree branches, but he had neither open injuries nor neurological deficits, although he sustained a right rib fracture and a neck sprain. Nuchal pain was persistent, but controllable. Three months after this accident, pain in the left nuchal region increased and he had a fever. Five days later, the neck pain became worse and swelling was noted in the left nuchal area. When the patient consulted a local hospital, his fever was 39.8°C and slight nuchal rigidity was noted. Tests revealed polymorphonuclear pleocytosis and an increased protein level in the cerebrospinal fluid (CSF). The diagnosis was acute bacterial meningitis. The patient was transferred to our institute for treatment.

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[1]Department of Neurosurgery and Division of Hyperbaric Medicine and [2]2nd Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan; [3]Department of Surgery, Ken-Ai Memorial Hospital, Onga-cho, Japan; and [4]Department of Internal Medicine, Tobata Kyoritsu Hospital, Kitakyushu, Japan.

Address all correspondence to Kiyotaka Kohshi, M.D., Department of Neurosurgery and Division of Hyperbaric Medicine, University Hospital of Occupational and Environmental Health, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan; e-mail: k-kohshi@clnc.uoeh-u.ac.jp

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On admission, the patient presented with swelling in the left posterior neck with tenderness, but neurological examination did not show any abnormalities except for mild nuchal stiffness. Hematological examination and blood chemistry revealed increased white blood cell count (13,300/mm^3) (normal, 4,000–9,000) and C-reactive protein (CRP) (26.8 mg/dL) (normal, <0.8 mg/dL) with neutrophilia and hypoalbuminemia (2.3 g/dL). CT scan of the neck could not confirm any intraspinal lesions except for muscular swelling in the left nuchal area. Chest X-ray showed a small amount of pleural effusion. Although no specific pathogen was identified in blood culture and CSF, the patient was given intravenous cefozopran hydrochloride 1 g every 6 hours. Despite parenteral antibiotic administration for 5 days, he began to complain of muscular weakness and paresthesia extending to the upper limbs, as well as urine retention. Cervical MRI demonstrated spinal compression along the anterior aspect of the thecal sac at the C1–C4 level, with an epidural lesion (Figure). Based on the clinical conditions and MRI findings, we made a tentative diagnosis of epidural abscess despite the absence of pathogens on culture.

We recommended that the patient undergo surgical decompression or drainage despite massive subcutaneous inflammation (cellulitis) in the posterior nuchal and paravertebral regions. However, we could not obtain the patient's consent for this treatment. Therefore, we added HBO therapy (250 kPa, 60 minutes of 100% oxygen inhalation; standard treatment regimen in our hospital) to the antibiotic regimen. HBO therapy was administered twice daily for 2 days, then continued daily for the first week, and 5 days per week thereafter. Three days after the beginning of HBO therapy, nuchal pain became controllable and CRP decreased to 17.9 mg/dL. Thus, we reduced the dose of cefozopran hydrochloride to 2 g per day. Thirteen days after the combined therapy was initiated, the patient no longer complained of motor and sensory abnormalities except for limited neck movement; laboratory data showed white blood cells (WBC) 4,700/mm^3 and CRP 0.5 mg/dL. MRI at that time showed marked regression of the epidural abscess. Because of the improving clinical conditions, intravenous antibiotic treatment was stopped and the patient was discharged from the hospital. He continued to receive HBO therapy for 5 days every week and oral administration of ampicillin 750 mg/day. After 7 weeks of combined therapy, the patient no longer complained of neck stiffness and MRI did not show any abnormalities. He continued oral antibiotic treatment with HBO therapy for 5

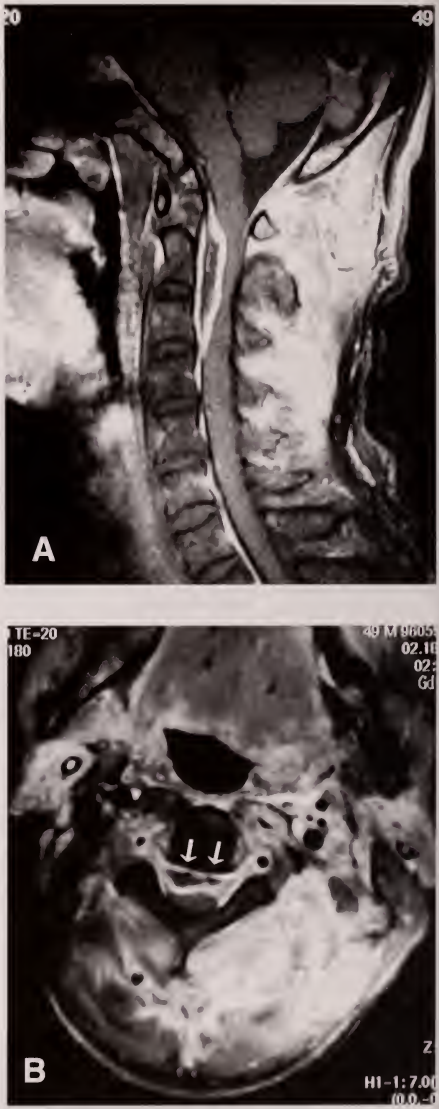

Figure. T1-weighted, sagittal and axial magnetic resonance images of the cervical spine with gadopentetate (Gd-DTPA) enhancement. **(A)** The sagittal image shows prominent contrast enhancement in the anterior epidural space, indicating epidural abscess, with a paravertebral abscess enhancing as well. **(B)** The axial image delineates the extent of the abscess cavity, also revealing contrast enhancement in the anterior epidural space and compression of the cord (arrows).

more weeks, and then he was followed without antibiotics. We stopped HBO therapy. On evaluation 6 months later, there was no recurrence of symptoms suggestive of a relapse of the epidural infection.

Discussion

The patient did not initially respond to antibiotics alone, and only after the addition of HBO therapy to the treatment regimen did his symptoms and laboratory data improve and the spinal lesion regress dramatically, as seen on MRI. This case thus illustrates the successful treatment of a cervical epidural abscess with antibiotics combined with HBO therapy.

Spinal epidural abscess is usually accompanied by back pain, localized tenderness, and high fever (12–14). The presence of radicular pain or a neurological deficit necessitates emergency diagnostic evaluation (4). MRI is now the diagnostic procedure of choice in most instances and does not require intrathecal injection of contrast material (13–15). *Staphylococcus aureus* is the most commonly reported pathogenic organism; common sources include cutaneous abscesses, sites of intravenous drug injection, and respiratory track infections (3, 4, 12, 14, 15). Non-penetrating spinal trauma may also cause a hematoma or inflammation susceptible to bacterial infection (3, 12, 14). In our patient, it is possible that cervical infection was secondary to trauma that spread into the epidural space. The initial symptom was pain in the left portion of the nape of the neck and the abscess was located mainly in the subcutaneous tissue.

Conventional treatment usually involves decompression of the abscess and the administration of an appropriate antibiotic therapy. Early diagnosis with sophisticated imaging techniques, prompt surgical intervention, and the introduction of effective antibiotics have gradually decreased mortality rates; however, the rates still hover around 12–20%, even in recent series (1–3).

Some of the major reasons for the poor outcomes associated with this disease are the following: (a) patients present with advanced cases because relatively early diagnosis is difficult; (b) pathological findings suggest that spinal cord infarction is attributable to thrombosis or thrombophlebitis of intra- and extramedullary veins; and (c) concomitant infective spondylitis (osteomyelitis or discitis) is present in most patients with spinal epidural abscess, even though it has not been observed on radiographic studies (2–4, 12, 16, 17). Although spondylitis is not one of the poor prognostic factors (1, 2, 14), intravenous antibiotic treatment is usually required for 4–8 weeks when spondylitis is present (4, 16). In addition, a factor complicating the use of antibiotics is the emergence of drug-resistant organisms, especially *S. aureus*, which is the predominant pathogen, with 15–25% of infections involving a methicillin-resistant strain (MRSA) (4, 18). A more recent report shows that more than one-third of isolated *S. aureus* infections were MRSA-positive (3). Under these circumstances, successful treatment with antibiotics alone is difficult, regardless of whether surgical intervention is performed.

To add HBO therapy to antibiotics is rare for the treatment of spinal epidural abscess. Ravicovitch and Spallone obtained good results for treatment of this condition with HBO therapy after laminectomy (19). They administered this therapy to improve neurological function after surgical intervention and not to treat the epidural abscess itself. Larsson et al., on the other hand, applied HBO therapy for the treatment of neurosurgical infections after cranial and spinal surgeries (20). Five of their seven patients with osteomyelitis and wound infections after spinal surgery showed resolution, with the use of combined therapy and without removal of foreign materials. However, to our knowledge, our present case is the first in which HBO therapy was used to treat primary spinal epidural abscess without surgical intervention.

HBO therapy has been used to treat a variety of infections and postoperative complications in bone and soft tissues. The suggested rationales of HBO therapy for infectious diseases are the following: (a) oxygen has an effect similar to antibiotics (even for aerobic bacteria), by impairing the bacterial metabolism; (b) the impaired bacteria-killing capacity of leukocytes in hypoxic surroundings improves with normoxia and is enhanced with hyperoxia; (c) the effects of some antibiotics are improved under hyperoxia; and (d) HBO therapy induces neovascularization, fibroplasia and bone remodeling (6).

Most infectious tissues are hypoxic because of ischemia secondary to inflammation-induced tissue edema. Also, in infectious osteomyelitic bones, oxygen partial pressure is very low (21). Recently the emergence of drug-resistant bacteria has become a serious problem in the control of many infected wounds. However, Larsson et al. presented a case of MRSA wound infection that could be cured by HBO therapy alone, without antibiotics (20). Their report suggests that HBO therapy is an efficacious option for the treatment of all bacterial infections, including those involving drug-resistant pathogens.

In summary, we have described a patient who underwent HBO therapy and antibiotics to manage primary spinal epidural abscess without surgical intervention. Although he failed to respond clinically to antibiotics alone, his clinical course improved after the introduction of HBO therapy. This case suggests that HBO therapy is an effective, noninvasive modality for the treatment of spinal epidural abscess.

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The Role of Patient-Controlled Apparatus for Sedation in the Emergency Department

ZEYNEP KEKEÇ, M.D.[1], AYNUR AKIN, M.D.[2], SEBNEM KILINÇ, M.D.[3] AND ERDOĞAN M. SÖZÜER, M.D.[3]

Abstract

Aim: Hand trauma is a fairly common cause of emergency unit admissions. Various analgesic and sedative agents are used to decrease pain and anxiety during minor surgical procedures for hand trauma patients and provide more comfortable conditions for the surgeon. The aim of this study was to investigate the potential role of patient-controlled sedation (PCS) during surgical procedures done under local anesthesia for hand trauma in the emergency department

Materials and Methods: Forty ASA I-II (Assignment of the American Society of Anesthesiologists) patients who visited the emergency unit with hand trauma were randomized to 2 groups of 20 patients each. The control group received 1 μg/kg of fentanyl (IV) and 0.028 mg/kg of midazolam (IV). Additional 1 mg doses of midazolam were given by the anesthesiologist to keep the sedation level between 3 and 4. In the PCS group, the midazolam was administered after programming the apparatus. The settings were as follows: loading dose: 0.028 mg/kg, bolus dose 1 mg, lock-out period: 5 min and basal infusion rate: 0. The loading dose was given before local anesthesia. All patients received prilocaine hydrochloride (Citanest 2%, 10 mL) for local anesthesia. The systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), oxygen saturation (SpO_2) and respiration rate (RR) were measured before intervention and at 2, 3, 5, 10, 15, 20 and 30 minutes.

Results: There were no differences in the demographic characteristics, operation and discharge times in the two groups ($p>0.05$). No cardiovascular or respiratory instability was observed in any patient, and SpO_2 remained over 95% for all. The SBP, DBP, HR and SpO_2 did not differ significantly ($p>0.05$). Although the sedation levels of all patients were satisfactory, the sedation levels of the control group were significantly lower at 5 and 15 minutes ($p<0.05$). The total midazolam dose was 4.3+1.1 in the control group and 4.0+0.8 in the PCS group. The patient satisfaction rate was 95% in the PCS group and 80% in the control group ($p>0.05$).

Conclusions: The two regimens did not differ with respect to hemodynamic changes, sedation levels and patient satisfaction. Therefore, PCS may be an acceptable alternative for surgical procedures performed using local anesthesia.

Key Words: Hand trauma, patient-controlled sedation, emergency department.

Introduction

HAND TRAUMA is a fairly common cause of emergency unit admissions. Various analgesic and sedative agents are used to decrease pain and anxiety during minor surgical procedures for these patients and to provide more comfortable conditions for the surgeon. The human hand provides the physical and physiological basis for creativity and precision through its mobility and sensation. It is also vulnerable to injury; an estimated 5% of emergency department visits are for the evaluation and treatment af hand injuries (1, 2).

Pain control is a vital component of the proper examination and treatment of acute hand injuries. Local anesthesia can be provided before close inspection, cleaning and surgical application, and repair of a wound or injury. For an extensive area of injury, a regional block can provide adequate anesthesia. If relaxation and systemic pain control are neeeded to care for a patient's injury, conscious sedation may be best (3).

Conscious sedation is a technique in which the use of drugs produces a state of depression of the central nervous system, enabling treatment to be carried out; verbal contact and protective reflexses are maintained. The technique has been widely used to supplement local anesthesia during exodontia, especially for very anxious patients (4).

Patient-controlled sedation offers the possibility of direct patient involvement in determining sedation requirements, in a manner similar to "patient-controlled anaesthesia" (5–7).

The aim of this study was to investigate the potential role of the patient-controlled sedation (PCS) device during surgical procedures performed using local anesthesia for hand trauma in the emergency department. We compared the effectiveness of patient-controlled sedation and emergency resident-controlled midazolam sedation, using a randomized prospective study.

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[1]Department of Emergency Medicine, Cukurova University Medical School, Adana, Turkey; Departments of [2]Anesthesiology and [3]Emergency Medicine, Erciyes University Medical School, Kayseri, Turkey.

Address all correspondence to Zeynep Kekeç, M.D., Kenan Evren Bulvarı, Toros Mah, 68.Sk, Seda Apt, A-Blok, Kat:3, No:26, 01170 Seyhan/Adana-Turkey; e-Mail: zkekec@cu.edu.tr

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Materials and Methods

This study was approved by the institutional review board of our hospital. Forty ASA I-II (Assignment of the American Society of Anesthesiologists) patients admitted for occupational hand trauma (ligament injuries and finger amputations) were included. Patients with only superficial skin and subcutaneous tissue cuts were excluded. All patients gave informed consent to participate. They were randomized to the intravenous sedation group (n=20) or the PCS group (n=20). The surgical procedures were performed by a second-year orthopedics resident. Follow-up was conducted by emergency room physicians.

A 22G Angiocath (Becton Dickinson Vascular Access, Sandy, UT) was placed in all patients. In the intravenous sedation group, patients were given 1 µg/kg of fentanyl and 0.028 mg/kg of midazolam, and the operation was performed using local anesthesia (Citanest 2%, 10 mL). The sedation level was monitored according to the Modified Observer's Assessment of Alertness/Sedation Scale (OAAS) (8) and additional 1 mg doses of midazolam were administered to maintain a sedation level of 3 to 4, as seen in Table 1.

The patient-controlled sedation apparatus enables the patient to adjust the level of sedation. Before the operation, the loading dose (the amount of drug required to induce initial sedation just after the apparatus is turned on), the bolus dose (the amount of drug the patient is allowed to self-administer at intervals), the lock-out duration (the interval during which the apparatus does not respond to the command of the patient), and the basal infusion rate (the amount of drug administered continuously) were set up. In the PCS group, midazolam was prepared at a concentration of 0.2 mg/dL; the loading dose was 0.028 mg/kg, bolus dose was 1 mg and lock-out time was 5 minutes. Basal perfusion was not given. All patients received instruction on using the apparatus. Before the operation and administration of local anesthesia, 1 µg/kg of fentanyl was administered and the loading doses were given via the apparatus.

Physicians evaluated each patient's affect, ECG, and respiration. Oxygen saturation (SpO_2) was monitored continuously by pulse oximetry for every patient. The systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiration rate (RR) were measured before intervention and at 2, 3, 4, 10, 15, 20 and 30 minutes. The time of discharge was determined according to the modified postanesthetic discharge scoring system (MPADSS) (9) (Table 2). The interval to MPADSS$\geq$ 9 was recorded as the time to discharge.

The sedation scores were evaluated by the Mann-Whitney U-test, and vital signs, operation time, and time to discharge were compared by the unpaired t-test. Probability values less than 0.05 were considered significant.

Results

A majority of the hand trauma patients had extensor tendon cuts and finger amputations. The distribution of the diagnoses in the two groups was similar.

There were no differences between the demographic characteristics or the operation and dis-

TABLE 1

OAAS (Observer's Assessment of Alertness/Sedation) Scores

Assessment Categories				
Responsiveness	**Speech**	**Facial expression**	**Eyes**	**Composite score Level**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (Alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more) slowing	3
Responds only after mild prodding or shaking	Few recognizable words	_	_	2
Does not respond to mild prodding or shaking	_	_	_	1 (Deep sleep)

TABLE 2

Modified Postanesthetic Discharge Scoring System

	Score
Vital Signs: When compared with initial evaluation	
20%	2
20–40%	1
40% or more	0
Ambulation: Patient can walk, no vertigo	2
Patient can walk with assistance	1
Patient can't walk, has vertigo	0
Nausea and Vomiting: Minimum	2
Moderate	1
Maximum	0
Pain: Minimum	2
Moderate	1
Maximum	0
Bleeding: Minimum	2
Moderate	1
Maximum	0
Total	**10**

charge times of the two groups ($p>0.05$) (Table 3). No cardiovascular or respiratory instability was observed in any patient and SpO_2 remained over 95% for all. The SBP, DBP, HR and SpO_2 did not show significant differences ($p>0.05$) (Figure). Although all sedation levels were satisfactory, the sedation levels of the control group were significantly lower at 5 and 15 minutes ($p<0.05$) (Table 4). The total midazolam dose was 4.3+1.1 mg in the control group and 4.0+0.8 mg in the PCS group. The patient satisfaction rate was 95% in the PCS group and 80% in the control group ($p>0.05$).

There was no evidence of cardiovascular or respiratory instability in either group. No patient in the PCS or the control group was sedated to a level deeper than full eyelid closure, with prompt response to verbal command.

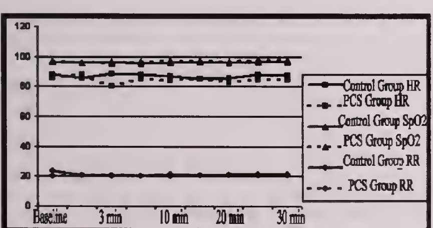

Fig. Correlation of some vital parameters between PCS groups and control groups.
PCS = patient-controlled sedation, HR = heart rate, SpO_2 = oxygen saturation, RR = respiration rate.

TABLE 3

Basic Characteristics of the Two Patient Groups

	Control Group (n=20)	PCS Group (n=20)	p
Age (year)	33±11	38±16	>0.05
Weight (kg)	72±7	72±10	>0.05
Length (cm)	170±2	171±5	>0.05
Operation time (min)	32.3±5	32.1±8	>0.05
Discharge time (min)	38.1±8	40.2±9	>0.05

PCS = patient-controlled sedation.

Discussion

A majority of the patients who visit the emergency department experience high levels of anxiety and severe pain. This situation becomes more problematic for patients who need to undergo minor surgical procedures. In addition, because of the pain and bleeding from the extremity, patients with hand injuries are very anxious about the possibility of limb loss. Sedation of these patients improves patient comfort and provides a more favorable setting for the physician. When applying local anesthesia, the physician uses analgesics and sedatives as he considers appropriate during the course of the procedure. The patient-controlled apparatus has been used successfully for postoperative pain treatment and for sedation in patients undergoing surgery under local anesthesia (10–14). However, we did not come across any studies on the use of the patient-controlled apparatus for the sedation and analgesia of hand trauma patients in the emergency department.

Lee at al. (15) compared PCS and IV sedation in elderly patients undergoing colonoscopy and concluded that PCS was safer. In another study, the PCS-treated group required significantly less medication when compared to a matched group of patients receiving conventional intramuscular treatment (16). Some studies compared the analgesic efficacy of

TABLE 4

Levels of Sedation. Mean (SD)

	Control Group	PCS Group	p
Initial	5.0±0.0	5.0±0.0	>0.05
1 min	3.45±0.68	3.50±0.51	>0.05
3 min	3.35±0.67	3.62±0.50	>0.05
5 min	3.35±0.67	3.93±0.25	<0.05
10 min	3.55±0.68	3.87±0.34	>0.05
15 min	3.65±0.58	4.06±0.44	<0.05
20 min	3.75±0.44	4.00±0.36	>0.05
25 min	3.95±0.22	4.00±0.0	>0.05
30 min	3.95±0.22	4.00±0.0	>0.05

PCS = patient-controlled sedation.

PCS with that of conventional treatments and found that with PCS more effective analgesia can be achieved with smaller amounts of opioid and that the frequency of side effects was lower (17–19).

Pac-Soo et al. (20) compared midazolam and propofol with PCS in patients undergoing cataract surgery under local anesthesia and concluded that both agents were appropriate and that midazolam allowed better control of blood pressure intraoperatively. Midazolam was used successfully in the present study. It is the benzodiazepene of choice, as it has a rapid onset and a short elimination half-life of 1.5–3.5 hours, and is void of significant pharmacolgically active metabolites (21). Midazolam is a popular drug for minor surgical procedure because of its minimal respiratory and cardiovascular depressant effects, amnestic properties, the absence of pain during its injection, and its short duration of action (13, 14).

Uyar et al. (10) used PCS in patients undergoing extracorporeal shock wave lithotripsy and compared the analgesic and sedative effects of alfentanil-propofol with those of alfentanil-midazolam. Patient satisfaction was high in both groups. Ghouri et al. (11) compared the perioperative efficacy of alfentanil, midazolam and propofol in patients undergoing minor surgical procedures under local anesthesia and reported equivalent results.

Zelcer et al. (21) compared PCS and conventional physician-controlled analgesia in patients undergoing vaginal ovum pick-up procedure and concluded that both methods were equally effective in terms of patient comfort and safety. In the present study, both methods achieved adequate sedation, patient safety and patient satisfaction.

Conclusion

PCS is a reliable method of sedation that ensures patient comfort. Administration of opioid analgesics in addition to local anesthesia to hand trauma patients undergoing surgical procedures significantly enhanced patient satisfaction. The lower amount of midazolam used, the higher level of patient satisfaction and the absence of major changes in cardiovascular and respiratory parameters and consciousness suggest that sedation with PCS may be an option for patients undergoing minor surgical procedures. However, PCS does not improve hemodynamic parameters and sedation levels, and PCS apparatus is required to be set up before the surgical application. Because of these conditions, PCS may not be very practical for use in the emergency room.

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Carbofuran Poisoning among Farm Workers

Salim Satar, M.D.[1], Serdar Satar, Ph.D.[2], Ahmet Sebe, M.D.[1], and Hasan Yesilagac, M.D.[1]

Abstract

Accidental or intentional ingestion of carbofuran can produce a life-threatening syndrome that requires prompt diagnosis and treatment. This paper investigates unintentional carbofuran poisoning in farm workers.

Thirteen patients were admitted to the emergency department with carbofuran poisoning between January 2002 and August 2004 (2 female, 11 male). The patients had been poisoned while mixing the liquid form of carbofuran with seeds. Their hands were red on admission. Complaints most commonly reported by the patients on admission were nausea, vomiting, headache, weakness, dizziness and blurred vision. The most commonly observed signs were tachycardia, tachypnea, salivation, miosis, elevated blood pressure, and fasciculation. Three patients were agitated and one was lethargic on admission. We reviewed the patients' medical charts retrospectively, as well as the demographic data, intoxication route, clinical and laboratory presentations, and outcomes. We made the diagnosis according to a compatible exposure history and clinical findings.

The most commonly observed laboratory finding was hyperglycemia, which was found in 6 patients. Serum pseudocholinesterase level was low in only one patient. All the patients were cured and discharged from the hospital in good physical condition.

Rapid onset, mild illness and quick recovery are typical characteristics of acute occupational carbofuran poisoning. We conclude that public health efforts should educate farm workers about the dangers of pesticide application so that its threat can be diminished.

Key Words: Carbofuran, dermal route, emergency, farm workers, poisoning.

Introduction

The carbamates are a group of salts or esters of *N*-substituted carbamic acid. They are used as agricultural and household insecticides. Aldicarb, carbaryl, propoxur, and carbofuran are the ones most commonly used. Carbamate insecticides differ structurally from organophosphorus esters, but both types inhibit acetylcholinesterase. Cholinesterase inhibition caused by carbamate is labile, reversible and of short duration (1).

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranylmethylcarbamate) is a carbamate insecticide used for the control of soil-dwelling insects in maize, oilseed rape, sorghum, sugar beet, sunflowers, vegetables and some fruits. It has two different formulations in the Turkish agricultural market. The first one has 35% active ingredient and is registered to use for seed application in corn and sugar beet. The second one has 5% active ingredient and is restricted for use in foliar application for sugar beet. Carbofuran is one of the metabolites of benfuracarb and was detected in fatal human cases following benfuracarb ingestion (2). Carbofuran inhibits cholinesterase and is metabolized rapidly and completely by hydrolysis in rats; it has been assigned to the Ib toxic class by the World Health Organization (3). Carbofuran was introduced by Bayer AG and is widely used in many countries, including Turkey.

Several cases of fatal poisoning by carbofuran following accidental ingestion have been reported (1, 4, 5). We describe 13 cases of unintentional carbofuran poisoning via the dermal route.

Patients and Methods

Thirteen adult patients poisoned with carbofuran were admitted to Cukurova University's School of Medicine, Department of Emergency Medicine, between January 2002 and August 2004. Relatives of the patients brought the bottles which contained the liquid carbofuran apparently used. The carbofuran concentration used by our patients was 35%. We made the diagnosis according to a compatible exposure history and clinical findings.

From the [1]School of Medicine, Department of Emergency Medicine and [2]Faculty of Agriculture, Department of Plant Protection, Cukurova University, Balcali-Adana/Turkey.

Address all correspondence to Salim Satar, M.D., Cukurova University, School of Medicine, Department of Emergency Medicine, 01330 Balcali-Adana/Turkey; email: ssatar@cu.edu.tr

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We also reviewed their medical charts retrospectively, as well as the demographic data, intoxication route, clinical and laboratory presentations, and outcomes.

Observations

From January 2002–August 2004, 13 patients were admitted to a university-based emergency department with carbofuran poisoning. Two of them were female and 11 were male. Two of the patients were farmers who own their own land; the others were employed as farm workers. Table 1 shows the demographic data and the complaints of the patients on admission to the emergency department. There was no pathologic finding or underlying disease in the medical history of any of the patients. All poisonings were unintentional, and the route of poisoning was dermal in all cases. The patients were poisoned while mixing the liquid form of carbofuran with seeds by hand, and their hands were red on admission. The complaints most commonly reported by the patients on admission were nausea (85%), vomiting (69%), headache (46%), weakness (31%), dizziness (23%), and blurred vision (23%). Table 2 shows the initial physical signs and clinical findings. The most commonly observed signs were: tachycardia (62%), tachypnea (54%), salivation (46%), miosis (31%), elevated blood pressure (23%), and fasciculation (11%). Three patients were agitated and patient #9 was lethargic on admission. The most commonly observed laboratory finding was hyperglycemia, found in 6 patients (Table 3). Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased minimally in patient #1 but returned to normal limits after two days. Blood urea nitrogen, creatinine and electrolytes were within normal limits in all cases (Table 3). Pseudocholinesterase (PSE) samples were obtained from all patients on admission. PSE level was low only in patient #9 (Table 3) and it returned to normal after 2 days. PSE was assayed in serum with enyzmatic colormetric process (Integra 800 Roche®) in our hospital's central laboratory, where results could be obtained in one hour.

All of the patients were hospitalized. After diagnosis they were decontaminated by clothing removal and showering. All patients received supportive therapy, including oxygenation, intravenous fluids, monitoring, and medications according to their symptoms. During hospitalization, patients 2, 3, 9, and 11 received atropine (Table 2). The length of hospital stay was 1–2 days (Table 2). All of the patients were cured and discharged from the hospital in good physical condition.

Discussion

Carbamate insecticides, like organophosphates, inhibit acetylcholinesterase and produce similar clinical manifestations of acute intoxication. There are two main pharmacokinetic characteristics that distinguish carbamates from organophosphates. First, carbamate insecticides do not easily cross into the central nervous system. Central nervous system effects of carbamates are thus limited, although central nervous system dysfunction may still occur

TABLE 1
Demographic Data and Patient Complaints

	Patients												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Age (Years)	19	38	42	44	42	24	33	47	32	36	35	25	27
Gender	Male	Female	Male	Male	Male	Male	Male	Male	Male	Male	Female	Male	Male
Season	Summer	Summer	Summer	Spring	Spring	Summer	Summer	Summer	Spring	Summer	Spring	Summer	Summer
Place of poisoning	Rural	Rural	Urban	Rural	Rural	Rural	Rural	Rural	Rural	Urban	Rural	Urban	Rural
Occupation	Farm W	Farm W	Farmer	Farm W	Farm W	Farm W	Farm W	Farmer	Farm W	Farmer	Farm W	Farm W	Farm W
Type of exposure	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten	Uninten
Route of poisoning	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal	Dermal
Onset of Symptoms (hours)	**6**	**4**	**3.5**	**3.5**	**6**	**6**	**4**	**6.5**	**1.5**	**7**	**5**	**5.5**	**7**
	Complaints at Onset												
Headache	+	-	-	-	-	+	-	+	-	+	-	+	+
Nausea	+	+	+	+	+	+	+	-	+	+	+	+	-
Vomiting	-	+	+	+	+	+	-	-	+	+	+	+	-
Dizziness	-	+	-	-	-	-	+	-	+	-	-	-	-
Weakness	-	-	-	+	-	-	+	-	+	-	+	-	-
Blurred vision	-	+	-	-	-	-	-	-	+	-	+	-	-

Farm W = farm worker; Uninten = unintentionally.

TABLE 2

Initial Physical Signs and Clinical Findings, Treatment, and Patient Outcome

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Temperature °C	36.4	36.7	36.5	37.1	36.4	36.5	36.6	37.0	36.8	36.4	36.7	36.5	36.4
Heart rate/minute	112	121	82	94	114	81	132	79	52	81	92	122	91
Blood pressure (mm Hg)	120/80	140/100	110/70	130/85	120/75	120/80	130/90	110/70	100/60	120/80	110/70	140/100	120/80
Respiratory rate/minute	14	18	17	19	15	15	18	14	24	18	14	22	13
Mental status	Awake	Agitated	Awake	Awake	Awake	Awake	Agitated	Awake	Lethargic	Awake	Awake	Agitated	Awake
Pupil size	Normal	Miosis	Miosis	Normal	Normal	Normal	Normal	Normal	Miosis	Normal	Miosis	Normal	Normal
Salivation	+	+	+	+	-	-	-	-	+	-	+	-	-
Fasciculation	-	+	-	-	-	-	-	-	+	-	-	-	-
Treatment	Support	Atropine	Atropine	Support	Support	Support	Support	Support	Atropine	Support	Atropine	Support	Support
Length of hospitalisation (days)	1	2	1	1	1	1	2	1	3	1	1	2	1
Outcome	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured	Cured

Support = supportive therapy.

TABLE 3

Laboratory Values of the Patients on Admission to the Emergency Department

	Patients												
	1	2	3	4	5	6	7	8	9	10	11	12	13
WBC (uL)	10,600	10,300	9,600	11,300	11,700	12,300	19,500	10,400	12,400	11,400	10,000	10,500	10,600
Hgb (g/dL)	14.0	9.5	13.5	14.1	15.7	14.4	14.5	13.8	15.2	10.5	13.1	12.9	14.1
Hct (%)	40.6	28.8	39.6	41.2	44.5	43.9	41.7	39.5	44.6	32.1	38.5	38.3	41.2
Plt (uL)	280,000	327,000	274,000	224,000	220,000	197,000	274,000	145,000	221,000	285,000	323,000	22,000	179,000
Glc (mg/dL)	124	152	95	101	138	96	177	102	93	87	92	125	112
AST (U/L)	59	16	17	18	17	31	23	27	34	21	19	15	32
ALT (U/L)	52	13	12	16	15	21	17	24	36	19	21	14	26
BUN (mg/dL)	21	18	11	13	13	17	20	16	12	14	17	19	22
Cr	1.3	0.7	0.6	0.8	0.9	1.1	0.7	0.6	0.8	0.9	1.0	0.6	0.7
Na (mmol/L)	145	136	141	142	139	142	138	138	139	141	140	144	139
K (mmol/L)	3.4	3.8	4.1	4.2	4.8	4.1	3.9	3.7	4.3	3.9	4.4	4.8	3.9
PSE (U/L)	11,373	6,854	7,542	9,541	10,421	10,753	7,848	11,575	4,132	10,457	8,745	9,653	12,654

WBC = white blood cell; Hgb = hemoglobin; Hct = hematocrit; Plt = platelet; Glc = glucose (normal range: 70–105); AST = aspartate aminotransaminase (normal range: 5–40); ALT = alanine aminotransaminase (normal range: >41); BUN = blood urea nitrogen (normal range: 8–25); Cr = creatinine; Na = sodium (normal range: 135–145); K = potassium (normal range: 3.5–5.1); PSE = pseudocholinesterase (normal range: 6400–15500).

after massive poisoning or may result from hypoxia secondary to pulmonary toxicity and respiratory muscle paralysis. Second, the carbamate-cholinesterase bond does not age, as in organophosphate poisoning; thus it is reversible, with spontaneous hydrolysis occurring within several hours (6). The result is briefer inhibition and less mammalian toxicity (1).

Carbofuran, an anticholinesterase carbamate, is commonly used as an insecticide, nematicide, and acaricide in agriculture practice throughout the world (7). It was first used commercially in 1967 and its use has grown rapidly over subsequent years (8). Its widespread use in agriculture is a potential source of contamination of food, water and air, and consequent health effects risks (7). It is widely used in Turkey, especially in the Mediterranean region. The patients studied here had not paid attention to the usage and safety instructions on the bottle. Specifically, they had mixed the seeds with the liquid carbofuran with their bare hands. That is how the poisoning occurred. Although the instructions for using the compound were written on the bottles, they disregarded them, perhaps due to their limited literacy, relative inexperience and/or lack of supervision.

Carbofuran is most lethal when ingested. Acute toxicity is directly associated with the size of the dose the organism receives (7). It is also highly toxic by inhalation, and moderately toxic by dermal absorption. Risks from exposure to carbofuran are especially high for persons with asthma, diabetes, cardiovascular disease, mechanical obstruction of the gastrointestinal or urogenital tracts, or those in vagotonic states (9). Symptoms of carbofuran poisoning include nausea, vomiting, abdominal cramps, diarrhea, excessive salivation, weakness, imbalance, blurring of vision, breathing difficulty, increased blood pressure and incontinence (8). Central nervous system abnormalities may occur in victims of severe carbamate poisonings, some of which may result from hypoxia caused by respiratory insufficiency or severe bronchorrhea (6). Complaints most commonly reported by our patients were nausea, vomiting, headache, weakness, dizziness, and blurred vision. The most commonly observed signs were: tachycardia, tachypnea, salivation, miosis, elevated blood pressure, and fasciculation. Only one of our patients was lethargic, and it may have been because of the length of exposure to the chemical and the concentration of carbofuran, since the PSE level was low only in that patient.

Our findings and the onset of the symptoms were similar to those of the patients reported by the Centers for Disease Control and Prevention (10). Their report mentioned that the patients had received supportive therapy; however, there was no information as to whether they were given atropine or pralidoxime. In our study, four of the patients received atropine in addition to supportive medication, because of co-existing symptoms such as salivation, fasciculation and miosis. The most commonly observed laboratory finding was hyperglycemia, found in 6 patients. Hyperglycemia, a nonspecific finding, has been reported many times in the literature (11, 12); it has been known to occur as a consequence of the increased accumulation of acetylcholine at the nerve endings following acetylcholine inhibition (13).

Clinical diagnosis of carbamate toxicity is based on the known or suspected history of carbamate use and the presence of cholinergic symptoms and signs. Isolated cases may be less recognizable, resulting in delays in diagnosis and treatment. Because cholinesterase inhibition by carbamates is rapidly reversible, cholinesterase testing may be unreliable in diagnosing carbamate poisoning (10). In our patients, carbofuran exposure was diagnosed as the cause of illness based on visual evidence (colored hands) and symptoms of cholinergic poisoning. However, laboratory evidence of cholinesterase depression was found in only one patient. Acetylcholinesterase inactivated by carbamates spontaneously reactivates with plasma elimination half-lives of 1 – 2 hours, with clinical recovery in several hours, and rarely in more than 24 hours (14). Without continued exposure, cholinesterase inhibition reverses rapidly, and in nonfatal cases, the illness generally lasts less than 24 hours (15). In our series the duration of onset of symptoms varied from 1.5 – 6 hours, and the length of hospital stay was 1 – 3 days. Only patient #9, with cholinesterase depression, was hospitalized for 3 days. Four of our patients needed atropine during therapy.

The use of agricultural pesticides in developing countries carries potential risks. Frequently, the farm workers who use these pesticides are either insufficiently literate, informed or experienced to be fully aware of the health hazards involved. We conclude that public health efforts should be made to educate farm workers about the dangers of pesticide application so that its threat may be diminished.

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Frequency and Mortality Risk Factors of Acute Adult Poisoning in Adana, Turkey, 1997–2002

GULSAH SEYDAOGLU, M.D.[1], SALIM SATAR, M.D.[2], AND NAZAN ALPARSLAN, PH.D.[1]

Abstract

Objective: The purpose of this study was to evaluate the data on acute adult poisoning over a six-year period at a university emergency department in Turkey and identify the risk factors of mortality.

Material and Methods: In this survey, data were collected from 2,229 adult patients admitted to the Emergency Department (ED) of Cukurova Medical Faculty, Adana, from January 1, 1997 to December 31, 2002.

Results: Of all emergency admissions during the six years, 1.6% were poisoned. Of the total poisoning cases, 725 (32.5%) were males and 1,504 were females. Mean age was 29.3±13.2 for males and 23.8±9.6 for females ($p=0.001$). A majority of the cases (76.4%) were attempted suicides. The attempted suicide ratio is higher for women (gender ratio: 2.4/1) and youths. Drugs were the most frequent cause of poisoning (59.0%) and pesticides were the second (26.4%). Psychoactive drugs were the most common agent (33.5%) among drugs, with their rate increasing each year. Eighty-seven patients died (3.9%): alcohol (methanol) was the most frequent cause of death (20.6%), followed by mushrooms (11.5%), carbon monoxide (10.3%) and pesticides (8.3%). More men than women died by poisoning (OR: 1.8 CI: 1.1–3.1). Gender, age, season, clinical status, initial emergency care and type of substance were significant risk factors for mortality.

Conclusion: Poisoning by psychoactive drugs was increasing each year of the study, but many drugs are not a serious risk factor for mortality. However, organic phosphorus is a serious risk factor for poisoning and mortality in this area. Providing satisfactory public and emergency staff assistance and education on the subject may reduce the mortality rate.

Key Words: Adult, mortality, poisoning, risk factors.

Introduction

IN DEVELOPED COUNTRIES, the annual incidence of both unintentional and deliberate human poisoning varies from 0.2–9.3 poison exposures per 1,000 population, and continues to increase annually worldwide (1). Acute adult poisoning usually results from attempted suicide and tends to be associated with low morbidity and mortality. Trends in poisoning have been changing in recent years, and the methods and substances used for self-poisoning have changed considerably over time (2–10). In many countries, especially in Western Europe and North America over the last two decades, the most common agents taken by adults have been drugs (4–20). In developing countries, unintentional and deliberate pesticide poisoning is probably the commonest cause of adult deaths (21). In an extrapolation from very limited data, the World Health Organization (WHO) estimates that 3 million pesticide-poisoning cases occur worldwide each year, with 220,000 deaths, most of which are intentional (22).

In Turkey's Cukurova region, one with large agricultural fields of about 675,000 hectares, usage of pesticides is very common. Adana, with its population of about 1,900,000, is the main city of this region. The major landholders of the region employ seasonal labor. Every year thousands of families from neighboring areas come to Adana in the spring and summer as migrant farm workers. Most of them are illiterate and are unfamiliar with the usage warnings written on containers, bottles, etc.

No satisfactory data on demographic characteristics of poison victims and substances ingested were provided by reports of the Turkish Health Ministry (THM). In general, however, the prevalence of poisoning in Turkey is estimated as 0.04% in 1995 (23). The average annual rate of suicide in Turkey from 1974–1998 was 2.2 /100,000, and a total of 28,408 suicide deaths were reported in that period (24). An emergency call center was established in 1997, called the "112 Emergency Service" (ES). Emergency statistics are collected by this unit and reported annually by THM. According to these reports, in 2002, 4.2% of all patients recorded by the ES were poisoned. Although this statistic represents only the cases administrated by ES, it is a sign that poisoning has become as im-

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From Departments of [1]Biostatistics and [2]Emergency Department, Cukurova University School of Medicine, Balcali/Adana, Turkey.

Address all correspondence to Gulsah Seydaoglu, M.D., School of Medicine, Department of Biostatistics, 01330 Balcali-Adana, Turkey; e-mail: gseyda@cu.edu.tr

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portant a problem for medical emergency centers in Turkey as it is in developed countries. However, a statistic such as this does not provide the type of substance, cause of poisoning and outcome of poisoning, parameters needed for making comparisons with other countries.

Determination of the demographic and etiology in poisoning cases, and risk factors of mortality has major importance for the treatment and management policy of this health problem. The aim of this study was to evaluate the data on acute adult poisoning and determine the risk factors of mortality for a six-year period in our emergency department.

Material and Methods

This study was conducted at the Emergency Department (ED) of Cukurova Medical Faculty in Adana, from January 1, 1997 to December 31, 2002. The adult emergency department of the university sees over 25,000 patients annually. The toxicology laboratory is not activated yet, so analytical confirmation of cases could not be performed.

It was a retrospective study, using data based on patient files for the period January 1997 to December 2002. Specifically, the data was based on a special form routinely completed for all poison cases by ED staff. Since the Ministry of Health has determined that it is necessary to report all poisoning cases, standard forms and files of these cases are completed by staff as accurately as possible. All patients are followed up by the staff until patients have no remaining risk (i.e., are cured). During the period studied, only 18 patients were discharged within one hour without follow-up because they did not show any serious physical signs or symptoms in their medical examinations. Another 18 were referred to intensive care (IC), and information was obtained for only 5 of them (who were cured). Thirteen cases referred to IC with no information about their outcome were excluded from the data when analyses were performed for risk of death. The rest of the patients were followed until they died or were totally cured. Data on self-poisonings recorded by the ED staff were classified according to the International Classification of Diseases (ICD-10) categories relevant at the time: suicides, unintentional poisonings and undetermined intent. Poisonings of undetermined intent were not included in this study; thus the classification includes two titles.

The data form includes information about age, sex, date of poisoning, time and method of arrival, type and amount of medical intervention (i.e., gastric lavage, IV support, antidotes) given in other health centers or in the ambulance before referral (initial emergency care or resuscitation), substance, cause of poisoning, level of consciousness, severity of poisoning, length of hospitalization, and outcome. This information is collected by interviewing the patient and relatives. In particular, causes of poisoning and amount of toxins are asked about in detail.

During the six-year study period, 2,488 patients over 14 years old were admitted to the ED because of acute poisoning. Pediatric cases and animal envenomations were not included in this study. One hundred and fifty-seven patients were excluded because of incomplete key data elements (gender, age, drug name and cause of poisoning); thus 2,229 patient were analyzed. There were no statistically significant differences according to gender, age and mortality ratio between the dropout patients and the study group. Since there were no significant differences between years, data were analyzed in total.

The toxins were classified into 7 groups: drugs, inhaled gases (mostly carbon monoxide), mushrooms, caustics, pesticides, alcohol/methanol (48 of 60 cases were methanol poisoning, 12 were alcohol) and unknown. For multivariate analyses, the toxin groups were gathered into 3 groups: drugs, agrochemicals (pesticides, rodenticides, and caustics) and others (carbon monoxide, mushroom, alcohol/methanol and unknown). The drugs were also categorized, as follows: analgesics, psychoactive drugs, anti-epileptics, cardiovascular drugs, multidrugs and others (antibiotics, antihistamines, anti-emetics, vitamins and hormones). A majority of the multidrug group was a combination of analgesic and psychoactive drug, followed by analgesic and other(s).

The patients were classified by the poisoning severity score developed by the International Programme on Chemical Safety, the Commission of the European Union, and the European Association of Poison Centers and Clinical Toxicologists (IPCS; EU; EAPCCT) into four groups: none, minor, moderate and severe. For statistical analyses "none" and "minor" groups were grouped together as "mild"; "moderate" and "severe" groups were grouped together as "severe" clinical status.

Statistical analyses were performed using the statistical package SPSS v 10.0. Continuous variables such as age, duration of hospital stay, and duration of time between poisoning and hospital arrival were analyzed by using student's t test or one-way analysis of variance (ANOVA) between groups. The categorical data between groups were analyzed by using the Chi square test; Odds Ratio and confidence interval (CI) were calculated by univariate analyses and multiple logistic regression analysis. Results were presented as mean ± SD and percent (%). A p value of less than 0.05 was considered significant.

Results

According to Ministry of Health (MH) statistics, trauma is the leading cause of admission to the emergency department in Turkey and poisoning ranked seventh. While the percent of causes of poisoning is decreasing in Turkey, it has been increasing in Adana over the last two years. This increase is also true for our emergency department (Table 1).

The distribution of age and gender is shown in the Figure. Of the total 2,229 patients, 62.2% were less than 25 years of age (range: 15–96). The mean age of the 725 males (32.5%) was 29.3±13.2 and the mean age of the 1,504 females (67.5%) was 23.8±9.6 (p=0.001). The patients' leading occupations were students, unemployed housewives, farmers, general service and unemployed.

Of the total, 1,614 patients (72.4%) were transferred from other health centers and only 13.3% of them arrived within 2 hours of poisoning. Also, 1,517 patients (68.1%) had not received any medical treatment, 549 had had lavage, 107 had received antidotes and 55 had received charcoal, 506 (22.7%) were unconscious and 18 (0.8%) were dead when they arrived at the ED. Eighteen patients were discharged following initial emergency care and 2,193 were hospitalized. The mean duration of hospitalization was 2.9±2.1 days. Thirty six patients (1.6%) were not followed, 19 (0.9%) were followed up for less than 12 hours, 287 (12.9%)

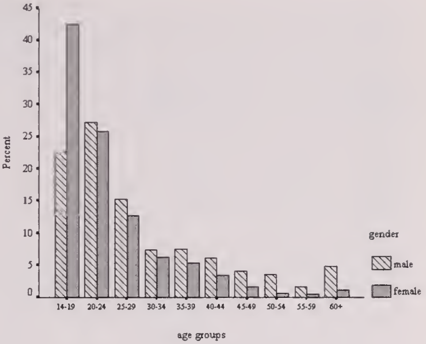

Figure. Distribution of age groups by gender in total poisoning cases (n=2,229).

TABLE 1

The Percent of Diagnoses of Diseases in Emergency Call Service According to Ministry of Health (MH) Statistics in Turkey and Adana by Years (1998–2002*)*

	Year				
	1998	**1999**	**2000**	**2001**	**2002**
Total number of cases	**98,716**	**137,224**	**211,944**	**268,594**	**350,056**
Pre-diagnosis of Diseases (Turkey)	%	%	%	%	%
Trauma	26.0	25.1	24.4	24.7	24.9
Cardio-vascular	20.6	21.0	20.8	21.6	21.2
Neurological	10.6	11.1	11.4	11.4	11.4
Respiratory	7.9	9.0	7.9	7.2	7.6
Psychiatric	6.0	6.1	7.1	8.3	8.1
Gastro-intestinal	5.0	4.7	5.0	4.6	4.6
Poisoning	*5.0*	*4.7*	*4.6*	*4.3*	*4.2*
Endocrine	2.4	2.6	2.8	2.9	2.9
Gynecological	2.0	2.3	2.3	2.2	1.9
Urinary	2.0	1.9	2.2	1.9	2.1
Infections	1.7	1.6	1.7	1.8	1.6
Neonatal	0.6	0.6	0.6	0.8	0.8
Other	10.2	9.3	9.2	8.3	8.7
Percent of Poisonings in Adana					
Data of MH	-	-	1.8	3.0	3.8
Data of present study	1.3	1.4	1.5	1.5	2.1

*The diagnosis of the MH emergency call service is based on paramedic staff's comments (physicians and nurses together) and not yet confirmed by a medical center or laboratory data. Data from 1997 is not available in MH.

were followed for 12–24 hours, 919 (41.2%) were followed for 24–48 hours and 968 (43.4%) were followed for more than 48 hours. Eighteen patients (0.9%) were referred to an intensive care unit, 69.6% were treated by IV supplements, 6.5% had lavage, 20.0% were given antidotes and 3.0% were given charcoal. Treatment of OPPs (organophosphate poisonings) includes decontamination and antidotal medication (2PAM [2 pralidoxime]) was used in all cases and atropine injections were used until bronchoalveolar secretion stopped). Three quarters of the patients needed psychiatric care, but only 8.2% were counseled by the Department of Psychiatry in ED. Sixty-nine hospitalized patients died, a total of 87 poisoning deaths, resulting in an overall mortality of 3.9%.

A seasonal difference was observed for rate of admission and poison substance. The number of patients increased in May (n=246, 11.0%) and June (n=226, 10.1%) and decreased in January (n=120, 5.4%) and February (n=136, 6.1%). The most common substance was pesticides in May and June and carbon monoxide in January and February.

Drugs were the most frequent cause of poisoning (59.0%) and organic phosphorus was second (26.5%). Carbamates and bipyridyliums were the most frequent organophosphates agents. Common clinical findings with these products were nausea, vomiting, abdominal pain, dizziness and headache.

Suicidal poisoning made up the majority of cases (76.2%); 13.4% of the patients were poisoned unintentionally and 10.4% were exposures (exposure and unintentional poisoning were grouped as unintentional). There were significant differences between the suicidal and unintentional poisoning groups by sex, age groups, season, clinical status and substance (Table 2). Of the 590 pesticide poisonings 47.6% were attempted suicides and 52.4% were unintentional cases.

The percent of mortality and severity for various types of toxins is shown in Table 3. Alcohol/methanol (20.6%) was the most frequent cause of death and severity. Mean length of hospitalization was longest for pesticide poisoning (4.2 days). The time lapse for arrival at the hospital for patients poisoned by mushroom was the longest (mean 9.9 hours).

TABLE 2

Characteristics of All Patients by the Cause of Poisoning in Adana, 1997–2002

		Cause of Poisoning			
	Risk Factor	**Suicide** n (%)	**Unintentional** n (%)	**Total** n (%)	**p value**
Gender	Male	494 (29.0)	231 (43.9)	725 (32.5)	
	Female	1209 (71.0)	295 (56.1)	1504 (67.5)	0.001
Age groups	14–19	635 (37.3)	166 (31.6)	801 (35.9)	
	20–24	468 (27.5)	118 (22.4)	586 (26.3)	
	25–29	233 (13.7)	69 (13.1)	302 (13.5)	
	30+	367 (21.6)	173 (32.9)	540 (24.2)	0.001
Year	1997–1998	602 (35.3)	198 (37.6)	800 (35.9)	
	1999–2000	512 (30.1)	152 (28.9)	664 (29.8)	
	2001–2002	589 (34.6)	176 (33.5)	765 (34.3)	0.6
Season	Winter	325 (19.1)	105 (20.0)	430 (19.3)	
	Spring	467 (27.4)	187 (35.6)	654 (29.3)	
	Summer	501 (29.4)	126 (24.0)	627 (28.1)	
	Autumn	410 (24.1)	108 (20.4)	518 (23.2)	0.001
Time of arrival	1–2 hour (early)	232 (13.6)	63 (12.0)	295 (13.2)	
	3+ hour (late)	1471 (86.4)	463 (88.0)	1934 (86.8)	0.3
Initial emergency care	Yes	570 (33.5)	140 (26.6)	710 (31.9)	
	No	1133 (66.5)	386 (73.4)	1519 (68.1)	0.003
Clinical status	Mild	1266 (74.3)	457 (86.9)	1723 (77.3)	
	Severe	437 (25.7)	69 (13.1)	506 (22.7)	0.001
Substance (toxins)	Drugs	1298 (76.2)	17 (3.2)	1315 (59.0)	
	Caustics	12 (0.7)	63 (12.0)	75 (3.4)	
	Pesticides	281(16.5)	309 (58.7)	590 (26.5)	
	Carbon monoxide	1 (0.1)	39 (7.4)	40 (1.8)	
	Mushroom	-	26 (4.9)	26 (1.2)	
	Alcohol/methanol	-	68 (12.9)	68 (3.1)	
	Unknown	111 (6.5)	4 (0.8)	115 (5.2)	0.001
Prognosis	Cured/transferred	1640 (96.3)	502 (95.4)	2142 (96.1)	
	Dead	63 (3.7)	24(4.6)	87 (3.9)	0.3

TABLE 3
Percent of Mortality and Severity of Poisoning, Time of Arrival and Hospitalization of Patients According to Substance (Toxin) (n=2,229)

Substance (Toxin)	% of Mortality	% of Severity	Mean Days of Hospitalization	Mean Hour of Arrival
Drug	1.5	22.1	2.4	6.1
Carbon monoxide	10.3	12.5	3.0	4.8
Mushroom	11.5	10.5	4.1	9.9
Caustics	1.4	4.0	2.8	7.4
Pesticides	11.9	45.6	3.7	5.6
Alcohol/methanol	20.6	22.1	2.6	5.9
Unknown	3.5	29.6	2.8	6.9
Total	3.9	22.7	2.9	6.1

TABLE 4
Trends in Poisoning-Related Drug Categories by Year in Adana, 1997–2002, with Percent of Mortality (n=1,315)

	Year				
Drug Categories	**1997–1998 n (%)**	**1999–2000 n (%)**	**2001–2002 n (%)**	**Total n (%)**	**Mortality n (%)**
Multidrug	160 (36.1)	129 (33.1)	137 (28.4)	426 (32.4)	7 (1.6)
Psychoactive	119 (26.9)	129 (33.1)	192 (39.8)	440 (33.5)	4 (0.9)
Analgesics	77 (17.4)	57 (14.6)	67 (13.9)	201 (15.3)	5 (2.5)
Anti-epileptics	35 (7.9)	33 (8.5)	38 (7.9)	106 (8.1)	1 (0.9)
Cardiovascular	16 (3.6)	23 (5.9)	28 (5.8)	67 (5.1)	1 (1.5)
Other	36 (8.1)	19 (4.9)	20 (4.1)	75 (5.7)	2 (2.7)
Total	***443(33.7)***	***390 (29.6)***	***482 (36.7)***	***1315***	***20 (1.5)***

Psychoactive drugs (33.5%) were the most common cause of poisoning, and the patterns of categories of drug poisoning have been changing over the years (Table 4).

The categories of psychoactive drugs were: tricyclic antidepressants (64.2%), benzodiazepines (16.9%), and psychotic and psychosomatic regulators (20.9%). Of the total 201 analgesics, 48.2% were non-steroidal anti-inflammatory agents (NSAIDs), 28.3% paracetamols, 11.2% salicylates and 12.3% other analgesics (metamizole, muscle relaxants, etc.). Of the total 426 multidrug poisonings, a majority involved a combination of antipsychotic plus analgesic (36.3%), followed by analgesic plus other(s) (24.1%).

Of the 87 patients who died, 18 (20.6%) were dead on arrival at the ED. To begin with, the risk factors of mortality, such as gender, age, year, season, clinical status, cause of poisoning, initial emergency care, time lapse for arrival, type of administration and type of substance, were evaluated by univariate analyses (Chi square test). The risk of mortality increased for patients who were older, male, unconscious, and transferred without medical intervention, and for patients who arrived after 2 hours ($p<0.05$). It decreased each succeeding year ($p<0.001$) but increased in winter ($p<0.001$). Cause of poisoning was apparently not a factor ($p=0.3$).

As a second step, the Odds Ratio and CI of risk factors for mortality were calculated by multivariate logistic regression analyses (Table 5).

Discussion

During the six-year study period (1997–2002), 2,388 poisonings accounted for 1.6% of the total admissions to the emergency department. The percentage of poisonings among the total number of emergency admissions was found to be 0.7% (25), 0.7% (26), 0.84% (27) and 5% (28) in studies held in Turkey. According to the Ministry of Health emergency statistics, the percentage of poisoned patients in Adana were 1.8, 3.0 and 3.8 respectively in 2000, 2001 and 2002. Considering the fact that our data does not include child and animal envenomations, the percentage of poisonings has to be higher than 1.6, which suggests that about half of the poisoning cases of Adana had been admitted to our ED. According to the annual report of the year 2000, 63 poison centers in the US reported that most exposures occurred at the patient's own residence, and that most patients

TABLE 5

*Number of Deaths Related to Poisoning in Adana, 1997–2002, using Multivariate Risk Factors of Mortality for All Death, Odds Ratio (OR) and (95% CI) (n=2,216)**

		Prognosis			
	Risk Factor	**Cured** n	**Dead** n (%)	**OR(CI)**	**p**
Gender	Female	1,456	39 (2.6)		
	Male	673	48 (6.7)	1.8 (1.1 – 3.1)	0.02
Age groups	14 – 19	775	23 (2.9)	Ref.	
	20 – 24	566	15 (2.6)	1.0 (0.5 – 2.1)	0.9
	25 – 29	294	7 (2.3)	0.7 (0.3 – 2.0)	0.6
	30+	494	42 (7.8)	2.9 (1.5 – 5.5)	0.001
Year	1997 – 1998	738	49 (6.2)	Ref.	
	1999 – 2000	650	14 (2.1)	0.22 (0.1 –0.4)	0.001
	2001 – 2002	741	24 (3.1)	0.58 (0.3 –0.9)	0.001
Season	Winter	404	22 (5.2)	Ref.	
	Spring	634	17 (2.6)	0.3 (0.1 –0.7)	0.006
	Summer	602	23 (3.7)	0.4 (0.2 –0.9)	0.04
	Autumn	489	25 (4.9)	0.6 (0.3 – 1.2)	0.2
Cause	Suicide	1,640	63 (3.8)		
	Unintentional	502	24 (5.8)	1.5 (0.8 – 2.9)	0.1
Clinical status	Mild	1,695	20 (1.2)		
	Severe	434	67 (13.4)	14.3 (8.0 – 25.5)	0.001
Time of arrival	Early (1 – 2 hour)	287	5 (1.7)		
	Late (>2 hour)	1,842	82 (4.3)	1.3 (0.5 – 3.6)	0.5
Initial emergency care	Yes	691	18 (2.5)		
	No	1,438	49 (4.6)	2.2 (1.2 – 4.1)	0.008
Substance toxin)	Drugs	1,288	20 (1.5)	Ref.	
	Organic Phosphorus	548	41 (7.0)	5.2 (2.8 – 9.8)	0.001
	Other	293	26 (8.2)	7.1 (3.4 – 14.9)	0.001
Total (n=2216)		**2,129 (96.1)**	**87 (3.9)**		

OR=Odds Ratio. CI=Confidence Interval, p value of risk factors for mortality calculated by multivariate logistic regression analyses.
*n=2,216, 13 cases referred to Intensive Care were excluded.

(75%) were managed on-site with assistance from a poison information center and did not require an emergency department visit (2). Taking into consideration the poisoning patients who are very often treated by traditional antidotal home remedies at their own residence, the number of poisonings according to hospital presentation data represent only the "tip of the iceberg" in this region also.

Mortality from poisoning was found to be 0% (26), 0.8% (27) 2.5% (29), and 2.8% (25) in various studies performed in Turkey. The mortality rate was found to be 2.9% in Greece (20), 1.4% in Hong Kong (30), 1.6% and 0.08% in Spain (31, 32), 0.5% in New Zealand (33), 0.03 in Belgium (19), 6.9% in Hungary (17), and 0.5% in 1987 – 1988 and 0.1% in 1992 – 1993, in the U.K. (7). To describe the trends in poisoning deaths in the U.S., health professionals in 11 states analyzed vital statistics data for 1990 – 2001. During this period, the death rate from poisoning in the U.S. increased 56%, from 5.0 per 100,000 in 1990 to 7.8 per 100,000 in 2001 (3). In another report it was shown that the accidental poisoning mortality rate has been increasing. In the U.S. in the 21-year period 1981 – 2001, mortality rates due to accidental poisoning more than doubled, from 2.0 per 100,000 in 1981 to 4.9 per 100,000 in 2001 (34). An overall mortality rate of 3.9% in our study is higher than in these studies. Our university hospital is the largest reference hospital in this region, and almost all neighborhood city hospitals and local hospitals refer their serious emergency cases to our hospital. However, the sizable percentage of patients transferred from other hospitals (72.4%) with serious clinical status (22.7%) and without initial emergency care (68.1%) end up with a high mortality rate.

As a result of the high rate of severely poisoned patients, our data concerning duration of hospitalization (2.9±1.8 day) is not in accordance with previous reports in some other countries (35, 36). However, the rate of referral to the intensive care unit is low (0.8%). According to a year 2000 annual report of 63 poison centers in the U.S. (total of 2,168,248 cases), 3% of patients required critical care (2). Decreasing mortality rate by years shows that university ED staff has learned to handle these cases.

Although the death rate for poisoning was higher for men than for women, and higher for older individuals than for younger ones, the prevalence of suicidal poisoning is higher for the young and for females, as mentioned in many other studies (3, 10–12, 15, 16, 18). In Utah, the death rates per 100,000 were higher for men than women during 1991–1998 and 1999–2003 (men: 1.86 and 4.90; women: 1.08 and 3.90), but the percentage increase in rates from 1991–1998 to 1999–2003 was greater for women than for men (261% vs. 163%) (37). More men than women die by suicide (gender ratio is 2.1 for this study); more women than men report a history of attempted suicide (gender ratio 2.4) (15, 16, 18, 27, 28). In 2001, the WHO reported that one million people commit suicide every year (38). Attempted suicides occur primarily among women, while completed suicides occur primarily among men (8, 13, 16, 39). It has been shown that women use significantly less violent methods than do men (39–41). The rates of attempted and completed suicides per 100,000 inhabitants over 15 years of age were found to be 31.9 and 9.9 for males and 85.6 and 5.6 for females, respectively, in a survey done in Turkey in 2002 (41). In another study, in the 4-year period 1998–2001, in a catchment area of Turkey, the mean annual suicide rate was found to be increasing (42). "This upward trend may be related to the intense economic difficulties, increasing unemployment, and rapid social change experienced in Turkey in recent years" (42).

Different trends in suicidal or unintentional poisoning rates were reported in some studies. The overall suicide rate has been falling since the 1960s in the UK (6, 16); however, the rate has been increasing in recent years for one notable group (young males, aged 15–24) (6, 7, 13, 16, 43). A linear increase was observed in unintentional poisoning mortality rates in certain Texas counties, and males were found to be at higher risk of death from accidental poisoning than were females (8). In this present study, no significant increase in suicidal or unintentional poisoning rate was found. However, a clear seasonal variation was seen in poisoning cases that may be due to agricultural poisoning (occurring in spring and summer) and psychotic disorders. It was reported that people who have psychotic disorders usually attempt suicide in the summer (44).

In Western Europe, North America and Turkey, drugs have been the most common agents taken by adults both for intoxication and for suicide (2, 4, 7, 13, 15–19, 20, 31–35, 45) but the trend in categories of drugs has been changing. There are variations from country to country, in Europe. In Finland, alcohol, cardiovascular drugs and psychotropic drugs are the most common causes of poisoning (35). Analgesic poisoning occurred more commonly than previously during 1976–1997 in UK (6, 16, 43). A similar pattern of change has been noted in Norway and in central Europe (45). In Turkey previous reports demonstrated that analgesics and NSAIDs are the most common causes of poisoning from drugs (25, 26). On September 16, 1998 the UK introduced legislation limiting the amount of paracetamol, salicylates and their compounds, which may have influenced both the number and severity of paracetamol overdoses in the U.K. (46). Before the 1990s, most drug overdose suicides involved barbiturates. However, since barbiturates became controlled drugs after the 1990s, their availability as a method of committing suicide significantly decreased (16). Thus, overdose with other psychotropic agents is now more frequent (3, 7, 12–14, 47). However, Backman et al. suggested that the increased number of sales of antidepressants has not caused an increased use of antidepressants in self-poisonings (15). Antidepressant overdoses, especially of selective serotonin reuptake inhibitors (SSRIs), were found to have increased substantially in many countries. In this study, drugs were the most common cause of poisoning. The increased incidence of poisoning by psychoactive drugs over the years might be due to the increased prescription of antidepressants. ED staff and primary medical care staff have an important role in recommending psychiatric care for people suffering from mental problems such as depression or for those who have attempted suicide or thought of doing so.

The demographics, sources and outcomes of methanol poisoning, which has a very high risk of mortality (20.6%), have not been described for Turkey. In a study of the recorded 30,485 calls concerning poisoning for Izmir from 1993 to 2002, 996 (3.3%) were found to be alcohol poisonings and 113 (0.37%) were methanol poisonings. Sixteen patients had died (48). Methanol used for producing cheap "eu de colognes" in Turkey is the principal reason for severe poisoning and deaths. In addition, in our region methanol is included in a traditional alcohol drink, which is produced cheaply and illegally, resulting in increasing mortality in recent years. Poverty is an important factor in mushroom and gas poisoning. The use of natural mushrooms instead of cultured mushrooms for meals as well as primitive, traditional coal stoves and flash heaters for heating frequently results in accidental poisoning.

Pesticides are the most common method of self-poisoning in many rural regions (25). Agrochemicals account for nearly 60% of all poisonings in Sri Lanka (mortality: 9.8%) (21), 46% in India (11), 35.8% in China (47), 31.4% in Zimbabwe (49), and 7.7% in Greece (20). The proportion of OPPs was found to be 15.1% (28) and 7.6% (25) in the ED of two universities located in agricultural cities in Turkey. In England and Wales, such agents account for less than 1% of hospital admissions due to poisoning (50). This is also the case in large industrialized cities in Turkey (0.9%) (26). Pesticides were responsible for only 1.1% of deaths from poisoning occurring in England and Wales between 1945 and 1989 (50). There were 338,170 poison exposures reported to poison centers in the United States over the 6-year period (1985–1990). Life-threatening manifestations or long-term sequelae occurred in 782 agricultural and horticultural chemical poisoning cases, and 97 deaths were reported (51). The death rate related to the agricultural poisoning has been found to be 0.4% (48) and 4.7% (28) in Turkey.

The frequency of pesticide poisoning (26.5%) and mortality (11.9%) was high in this study. Workers in agriculture, who are relatively poor and uneducated, migrate from southeastern of Turkey to Adana seasonally and live in tents that generally do not have a clean water supply. Pesticide application without adequate protection, illiteracy, economical problems, difficult life conditions and various psychological stresses seem to correlate with high rates of pesticide poisoning, both suicidal and unintentional. The high proportion of OPP poisoning patients transferred to the university hospital without antidotal treatment led us to consider that ED staff working in state hospitals may not be aware of the clinical manifestations and the antidotal treatment for this type of poisoning.

Limitation of the Study

Information about the outcome of 18 patients who were referred to IC was obtained only for 5 patients (cured). These were all fairly serious cases and may increase the death rate. These cases were excluded from the data when analyses were performed for risk of death. Since the toxicology laboratory has not been activated yet, analytical confirmation of cases was not possible; so the presumed diagnosis relied only on history, physical signs and symptoms. Although the history and physical examination are important, they may be unreliable or incomplete. Taking these factors into consideration, the family members, friends and the patient were questioned in detail, and the patients were followed up for at least 24 hours in the observation room as a departmental procedure. This procedure may have been a factor prolonging the duration of hospitalization.

Conclusion

Death was directly related to product toxicity and the severity of the poisoning. The study implicates pesticide poisoning as a serious risk factor for mortality in our region. There was also a clear relationship between fatal outcome and a delay between ingestion and medical support. Product toxicity, severity of the poisoning and a delay in medical support may be considered major predictors of a negative prognosis of the poisoning. We also conclude that evaluating the etiological and demographic characteristics of the patients and current toxicological trends has importance for the prognosis of these patients in emergency centers. Finally, it is clear that greater interdisciplinary collaboration is needed on this issue. Education of the public and also emergency department staff about appropriate initial emergency care and the crucial importance of transferring patients rapidly would reduce the mortality rate.

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Spontaneous Cholecystocutaneous Fistula Presenting with an Abscess Containing Multiple Gallstones:

A Case Report

Serdar Yüceyar, M.D., Suphan Ertürk, M.D., Ilhan Karabiçak, M.D., Ender Onur, M.D., and Fatih Aydoğan, M.D.

Abstract

Spontaneous cholecystocutaneous fistula is a rare complication of chronic calculous cholecystitis. This complication, a result of the natural history of gallbladder stones, was formerly common. Today it is rare, because of early diagnosis and treatment of biliary tract diseases. We report a case of spontaneous cholecystocutaneous fistula in a 70-year-old female patient who presented with an abscess formation in the right upper quadrant. After the incision of this infective focus, many gallstones were picked up. One-stage open cholecystectomy and excision of the fistula tract were carried out after control of the abdominal wall infection.

Key Words: Cholecystocutaneous fistula, cholelithiasis, biliary fistula.

Case Report

A 70-YEAR-OLD WOMAN was admitted to our hospital with complaints of erythematous swelling and pain of the right upper quadrant for eight weeks. She had a history of abdominal tuberculosis 40 years earlier and had had gallstones for 8 years. At physical examination, no pathology was determined except for an 8x4 cm erythematous swelling and tenderness of the right upper quadrant. The ultrasonography and computed tomography (CT) identified a gallbladder full of small stones adhering to the abdominal wall. An abscess formation including calculi and phlegmon was detected in the abdominal wall. The CT showed subcutaneous edema of the abdominal wall radiating to the right iliac fossa, but the physical examination showed no related findings.

A small incision was performed to the fluctuating area of the abscess. At first, 2–3 cc purulent material and several small gallstones drained from the incision (Fig. 1). No evidence of tuberculosis or malignancy was detected in the microbiologic and histopathologic examination of this focus. Initial treatment included local control of septic focus and broad-spectrum antibiotics administration. The inflammation subsided within 12 days, and 80 small gallstones were removed from the fistulous tract. Laparotomy was performed on the 12th day, using a right subcostal incision far from the fistula tract. At laparotomy, the fistula formation between the abdominal wall and the fundus of the gallbladder was also exposed (Fig. 2). Cholecystectomy and excision of the fistula tract were performed. The total number of stones reached 549 after

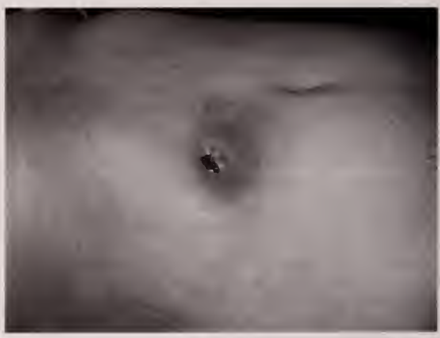

Fig. 1. Draining small gallstones after incision of the abscess on right upper quadrant.

From Istanbul University, Cerrahpasa Medical Faculty, Department of General Surgery, Istanbul, Turkey.

Address all correspondence to Ilhan Karabiçak, M.D., 523 W 160th Street #3D, New York, NY 10032.

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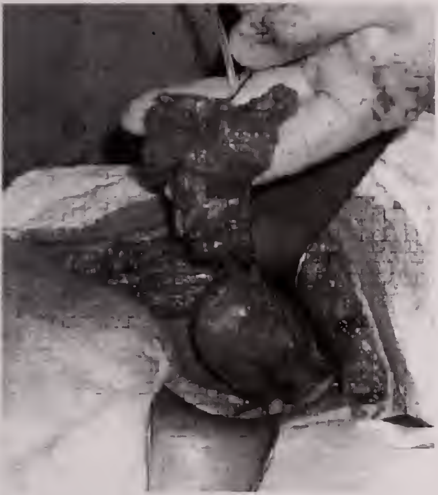

Fig. 2. At laparotomy, the fistula formation between the abdominal wall and fundus of gallbladder.

adding the stones remaining in the gallbladder. Postoperative recovery of the patient was uneventful.

Discussion

Spontaneous cholecystocutaneous fistula was a common complication of chronic calculous cholecystitis until the beginning of the twentieth century. Thilesus was the first to report a case of external biliary fistula in 1670 (1). Courvoisier described 169 cases in 1890. In 1949, Henry and Orr collected a total of 205 cases of external biliary fistula, adding 36 new cases to Courvoisier's report. In the past 54 years, 21 additional cases were reported in the literature (1–8).

Spontaneous perforation of the calculous cholecystitis to the abdominal viscera (internal fistula) is a not uncommon complication. While the common sites are the duodenum (77%) and colon (15%), perforation is rarely seen in the bronchial tree, stomach or urinary tract (3). Cutaneous external fistula is a rare presentation of patients with cholelithiasis. A case of spontaneous cholecystocutaneous fistula due to acalculous cholecystitis was reported by Chang et al. (5). Another case which was uncomplicated by gallstones was reported by Birch. It was suggested that the associated circumstances or conditions, such as steroids, polyarteritis nodosa, typhoid, bacterial dissemination and trauma, may be predisposing factors (8). Urban et al. reported a case of spontaneous cholecystocolonic and cholecystocutaneous fistula in association with stones and gliomatosis of the gallbladder (3). Internal and external fistula formation are a result of chronic perforation of the gallbladder. However, obstruction of the cystic duct, with (frequently) a calculus or (uncommonly) a carcinoma plays an important role in the pathophysiology of perforation. The adherence to the abdominal wall and necrosis of the gallbladder wall lead to fistula (2, 3). We considered that a history of abdominal tuberculosis diagnosed 40 years ago might have been the initial factor for the cholecystocutaneous fistula formation in our patient, but there was no evidence of tuberculosis in preoperative investigations.

The clinical presentation of cutaneous biliary fistula is variable and depends on its anatomical course. The external fistulas more frequently drain to the right superior quadrant and right flank or to the umbilicus. The opening of the fistula tract in the left-side costal margin, right-side iliac fossa, right groin and right gluteal region have also been reported (3). A painless draining sinus tract is the most common finding in these patients. Most of the patients are older than 50 years old, are women, and have a history of chronic biliary tract disease symptoms. The erythematous skin lesion in the right upper quadrant may be a patient's only presentation. However, skin lesions may lead to misdiagnosis (e.g., as a simple cellulites) or late diagnosis (5). In our patients, a soft tissue swelling and abscess formation in the right upper quadrant of the abdomen had been undiagnosed for eight weeks.

Ultrasonography and CT can be used for diagnosis of biliary tract pathologies and associated skin lesions. In the presence of a fistula opening, a fistulogram is necessary for the confirmation of communication with gallbladder or biliary tract. However, we did not need to perform a fistulogram on our patient, because the ultrasonography revealed gallbladder adherence to the abdominal wall and a tract between the gallbladder and right upper quadrant full of microcalculi. We also observed that the characteristic biliary calculi drained after incision of the abscess (Fig. 1). Eighty calculi were picked up during the treatment of this septic focus. The total number of biliary calculi in our patient was 549.

These fistulas are like a cholecystostomy. In high-risk patients, percutaneous removal of the stones and spontaneous closing of the fistula can be considered (9). Laparoscopic cholecystectomy was suggested as a feasible procedure by Mathonnet et al., but it has a high conversion rate (6).

After the control of acute inflammation in the abdominal wall, an elective open cholecystectomy with the excision of the fistulous tract appears to be the standard approach for efficient treatment today. If there is an unusual skin lesion in patients, especially older women with a long-standing history of calculous cholecystitis, external fistula formation must be considered as a possibility.

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Intestinal Obstruction Due to Rectal Endometriosis

Melih Paksoy, M.D., Ilhan Karabiçak, M.D., Fadil Ayan , M.D., and Fatih Aydoğan, M.D.

Abstract

We report a case of a premenopausal woman with severe constipation causing intermittent obstruction. Colonoscopy revealed a tight rectal stricture; however, mucosal biopsies were normal. Exploratory surgery revealed an intense fibrotic reaction involving the rectum and uterus, necessitating a simultaneous low anterior resection and hysterectomy. Pathology established a diagnosis of endometriosis.

Preoperative diagnosis of rectal endometriosis can be difficult to establish. Endometrial deposits do not invade the mucosa; therefore, colonoscopy with biopsies are frequently non-diagnostic.

Surgery may be the only definitive way to obtain a certain diagnosis. In cases involving rectal strictures of unknown etiology in premenopausal women, rectal endometriosis must be included in the differential diagnosis.

Key Words: Rectal endometriosis, intestinal obstruction, surgery.

Introduction

Endometriosis is defined as an ectopic proliferation of endometrial tissue outside the uterine cavity. Two causative mechanisms have been proposed: (a) canalicular transport of endometrium shed during menstruation and (b) growth of celomic epithelium into the myometrium of contiguous organs (1, 2).

Bowel involvement in endometriosis is usually localized to the rectosigmoid, sigmoid or upper part of the rectum, and less frequently to the cecum and right side of the colon. Endometriosis rarely affects the rectum circumferentially (3, 4). Colorectal endometriosis may cause obstructing symptoms difficult to distinguish from malignant or inflammatory disease (5, 6). We report a case of rectal endometriosis in a patient suffering from constipation; the condition was discovered only after the appearance of intestinal obstruction.

Case Report

A 36-year-old gravida 1, para 1, premenopausal woman was admitted to our hospital complaining of constipation, small stools, lower abdominal pain, and intermittent rectal bleeding over a 1-year period. She had previously been well, with a good appetite and no weight loss. Her basic blood tests were normal. She underwent a barium enema, which demonstrated a suspicious narrowing at 9 cm from the anal verge. Colonoscopy revealed almost complete stenosis of the rectum, which did not allow further passage of the scope. Biopsy specimens at the stenosis demonstrated histologically normal mucosa.

Pelvic computed tomography (CT) showed a 2×1.5 cm mass at the anterior portion of the rectum (Fig. 1). The patient underwent laparotomy for rectal stricture of unknown etiology. The rectum was circumferentially firm with tumor-like consistency. There was an intense fibrotic reaction involving the posterior wall of the uterus and the rectum, but the ovaries and Fallopian tubes were intact. Because a dissection could not be carried out safely, a low anterior resection and hysterectomy were performed. Grossly, the opened rectal specimen had polypoid projections protruding into the lumen and irregular mucosa beneath this area (Fig. 2). Microscopic evaluation revealed hyperplastic

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Department of General Surgery, Cerrahpasa Medical Facility, Istanbul University, Istanbul, Turkey.

Address all correspondence to Ilhan Karabiçak, M.D., 523 W160th Street #3D, New York, NY 10032; ikarabicak@yahoo.com

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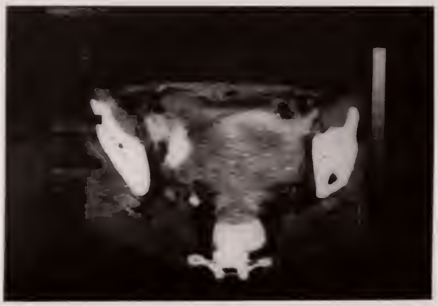

Fig. 1. Axial CT section with intravenous and rectal contrast section shows a 2×15 cm mass at the anterior portion of the rectum. Note the small nodular density in the right perirectal fat.

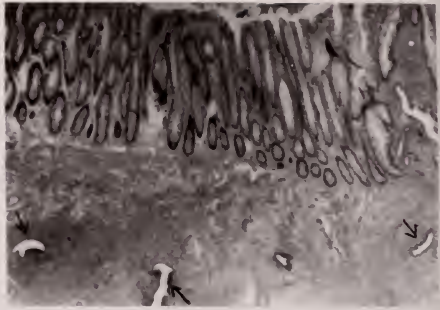

Fig. 3. Endometriotic glands and stroma within the submucosa and muscularis mucosa (arrows). (H&E × 100).

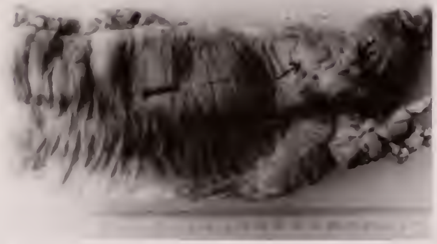

Fig. 2. Marked thickening of the rectal wall, with polypoid projections in the mucosa (arrows show hyperplastic polyps).

polyps and pseudopolyp formations together with typical endometrial glands, surrounded by some stroma infiltrating all layers of the rectum wall from serosa up to submucosa (Fig. 3). There was no sign of malignancy and no involvement of the lymph nodes. These findings led to the diagnosis of rectal endometriosis. On the 12th postoperative day, a rectovaginal fistula developed. Pelvic examination revealed a 0.5 cm fistula. The patient was restricted to a clear liquid diet with conservative management. The fistula closed spontaneously by postoperative day 26. At 4-year follow-up, she remains well without complaints.

Discussion

It has been estimated that 4 – 17% of all menstruating women have endometriosis (7, 8); 3 – 34% of these cases involve the gastrointestinal tract. The rectum and rectosigmoid junction together account for 70 – 93% of all intestinal endometriosis (3, 4).

The pathogenesis of endometriosis is unknown; however, the most widely accepted theory proposes retrograde menstruation and subsequent implantation on the peritoneum and pelvic viscera. Implants adhere to the intestinal serosal surface and may invade through to the submucosa (9). Colonoscopy and barium enema typically only show a stenotic lesion with intact mucosa, which is occasionally exacerbated during menstruation (5, 6).

Conventional biopsy forceps, especially those in use with fiberoptic instruments, take only superficial samples. The absence of mucosal involvement prevents an exact diagnosis by means of biopsy. This explains the difficulties of establishing the diagnosis preoperatively (10, 11). Pelvic or abdominal CT may visualize a thickened bowel wall, which often adheres to the uterus or uterine adnexa (5).

Although most gastrointestinal endometriosis is thought to be asymptomatic, symptoms may include crampy abdominal pain, dyschezia, tenesmus, abdominal distention, vomiting, diarrhea, constipation, melena or hematochezia, and may vary depending on the site(s) of involvement (3, 4).

Patients may also experience the classic pelvic endometriosis triad of dysmenorrhea, dyspareunia and dyschezia, as well as impaired fertility (12). As many as 40% of patients experience symptoms in a cyclic manner (13, 14); the symptoms can occur on a chronic or intermittent basis and may be unrelated to menstrual cycles (15, 16).

Endometriosis of the gastrointestinal tract may mimic a wide spectrum of diseases, including infectious etiologies, ischemic enteritis/colitis, inflammatory bowel disease and neoplasm (17).

Colonic endometriosis may manifest as an acute abdomen resulting from perforation and associated peritonitis (18). Small intestinal endometriosis may produce vague symptoms such as abdominal pain and bloating. Involvement of the ileum frequently results in the development of small bowel obstruction (19). The true incidence of endometriosis causing bowel obstruction is unknown, although complete bowel obstruction is particularly rare in cases of large bowel endometriosis (16).

Patients with endometriosis in the muscularis propria are more likely to have obstructive symptoms resulting from adhesions, masses and strictures rather than symptoms suggestive of colitis. Serosal endometriosis may elicit a marked acute and chronic inflammatory infiltrate and an organizing serositis with adhesions (17).

Malignancy can arise in any extragonodal site of endometriosis. Hyperestrogenism, either endogenous or exogenous, has been implicated as a risk factor for the development of cancer from endometriosis (20–22). The most common sites are in the pelvic peritoneum, rectovaginal septum, vagina and colorectal serosa. Among endometriosis-associated intestinal tumors, the rectosigmoid colon is the most common site (17, 22). Endometrioid intestinal tumor has symptoms similar to those of intestinal adenocarcinomas, such as abdominal and/or pelvic pain and pelvic mass, especially if the patient has been treated with hormone replacement therapy (23).

Preoperatively, this patient gave no history of menstrual irregularity, nor did she describe any relationship between the pain, hemorrhage, and menstrual cycle. However, when she was questioned again postoperatively, she agreed that the pain was more severe at the time of her periods. Furthermore, it was discovered that she had previously undergone diagnostic laparotomy for infertility.

As mucosal invasion by endometrioma is quite rare, an accurate diagnosis is often difficult to make without surgery. For our patient the stenosis could not be diagnosed correctly by barium enema, colonoscopy, biopsy or CT.

In this case, there was no dissection plane between the rectum and uterus, since all layers of the rectal wall from serosa to submucosa were infiltrated. Another case involving simultaneous low anterior resection and hysterectomy for rectal stenosis in a premenopausal woman has been reported. Similarly, this diagnosis of endometriosis was made postoperatively on histology (24).

Conclusion

Rectal endometriosis may present as a severe stricture leading to obstructive symptoms. The diagnosis can be difficult to establish preoperatively due to the submucosal location of the lesion. Surgical intervention may be the only definitive way to obtain a certain diagnosis. In cases involving rectal strictures of unknown etiology in premenopausal women, rectal endometriosis must be in the differential diagnosis.

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Acute Myocardial Infarction after Hydrochloric Acid Ingestion

Sedat Yanturali, M.D., Ersin Aksay, M.D., and Ridvan Atilla, M.D.

Abstract

We report a case of acute ST segment elevated myocardial infarction associated with hydrochloric acid ingestion. Severe systemic acidosis developed shortly after massive hydrochloric ingestion; it was complicated by the presence of acute myocardial infarction. A new complication of acid ingestion is presented and a possible mechanism is discussed.

Key Words: Corrosive, myocardial infarction, hydrochloric acid ingestion, acidosis.

Introduction

Acid ingestion causes gastric and intestinal perforation and upper gastrointestinal hemorrhage. Significant acute exposures may cause metabolic acidosis, hemolysis, renal failure, and fatality (1). To our knowledge, acute myocardial infarction (AMI) associated with hydrochloric acid ingestion has not been yet reported in the medical literature. We present the first reported case of fatal hydrochloric acid ingestion complicated with ST segment elevated AMI.

Case Presentation

A 63-year-old female presented at the emergency department (ED) after ingesting domestic cleaning solution containing hydrochloric acid. She stated that she had ingested 250 mL of liquid acid of unknown concentration in a suicide attempt an hour earlier. She was brought to the ED by relatives, complaining of epigastric pain. Her medical history included primary coronary intervention and stent implantation to the left anterior descending coronary artery because of acute anteroseptal myocardial infarction nine months earlier. She had been taking aspirin, metaprolol and meprobamate, and was also being treated with venlafaxine and mirtazapine for major depression.

The patient's vital signs at the ED were as follows: blood pressure 153/87 mm Hg, pulse rate 86 beats/minute, respiration 34 breaths/minute, and pulse oximetry 97%. She was perspiring and appeared anxious. The patient was placed on a cardiac monitor, after which morphine was administrated intravenously for severe epigastric pain. Examination revealed oropharyngeal erythema and epigastric tenderness. Cardiovascular examination revealed normal S1 and S2. All the peripheral pulses were normal and the lungs were clear bilaterally. The remainder of the patient's physical examination was also normal. A nasogastric tube was placed; bright red drainage was observed after gastric lavage and suction. Initial electrocardiogram (ECG) revealed QS in leads V1 to V3 without ST segment or T wave abnormality (Fig. 1). Chest x-rays showed no evidence of mediastinitis or subdiaphragmatic free air, nor increased cardiothoracic ratio or congestion. Laboratory studies, including complete blood count, electrolytes, and kidney function tests, were within normal limits, except for leukocytosis (white blood count: 21,000/mm^3) and hyperchloremia (Cl: 114 mmol/L). Myoglobin level was slightly high (109.8 ng/mL, normal range: 0.00 – 72.00 ng/mL) but other cardiac markers (troponin T, creatine kinase and CK-MB) were normal. Arterial blood gas (ABG) analysis exhibited metabolic acidosis. Sodium bicarbonate replacement was initiated and endoscopy was planned. Serial ABG analysis and hematocrit levels with clinical course are shown in the Table.

From Dokuz Eylul University Hospital, Department of Emergency Medicine, Izmir, Turkey.

Address all correspondence to Dr. Sedat Yanturali, Dokuz Eylul University Hospital, Department of Emergency Medicine, 35340, Inciralti, Izmir, Turkey; e-mail: sedat.yanturali@deu.edu.tr

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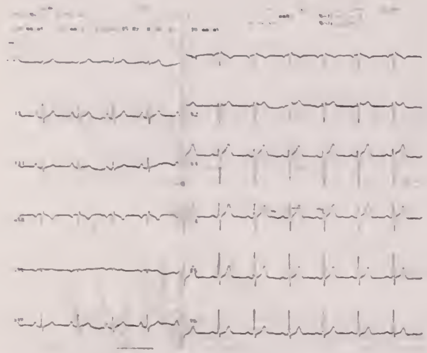

Fig. 1. Initial ECG revealed QS formation in leads V1 to V3 without ST segment or T wave abnormality.

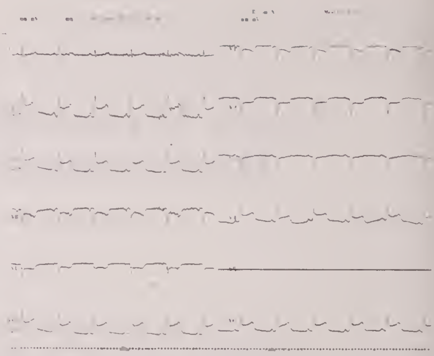

Fig. 2. ECG during the chest pain showed ST segment elevation at inferolateral leads consistent with acute ST segment elevation myocardial infarction.

The patient suffered severe chest pain one hour after presentation to the ED. The ECG showed ST segment elevation at inferolateral leads and AMI was diagnosed (Fig. 2). Nitroglycerine, metaprolol, and clopidogrel were administered, after which she underwent percutaneous coronary intervention. The coronary angiogram had revealed 80% luminal narrowing in both the right coronary artery and left anterior descending artery, without intraluminal thrombus. TIMI III flow was detected in all coronary arteries. There was no post-procedure intracoronary occlusion, so no further intervention was undertaken. After coronary angiography, ST segment elevation decreased to 0.5 mm on ECG (Fig. 3). The patient was transferred to the coronary care unit (CCU).

The patient's condition continued to deteriorate during her hospital stay. Despite administration of sodium bicarbonate (total dose of 300 mEq), lactic acidosis was persistent (lactate: 2.9 mmol/L, normal: 0.55 – 1.75 mmol/L). She devel-

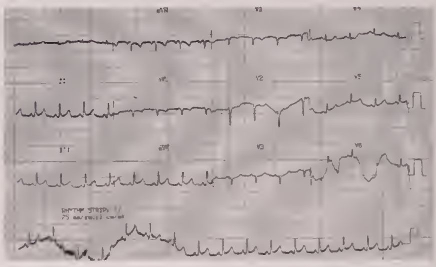

Fig. 3. After coronary angiography, ST segment elevation decreased to 0.5 mm.

TABLE

Serial ABG Analysis and Hematocrit Results with Clinical Course.

Time (hour)	First hour	2nd	3¹/2 hours	4th	4¹/2 hours
Hospital Course	Emergency Department		Coronary Angiography Unit	Coronary Care Unit	
Clinical course	Epigastric pain	Chest pain with ST segment elevation	ST segment normalization without coronary intervention	Intubation	Death
pH	7.28	7.14	7.04	6.94	* 7.38
HCO_3 (mmol/L)	13.8	9.4	10.8	7.4	21.6
Base excess (mmol/L)	−13.1	−17.5	−18.4	−23.0	−2.4
Potassium (mmol/L)	4.4	4.4	5.9	6.5	5.8
Hematocrit (%)	48	41	30	33	25

* After administration of 130 mEq $NaHCO_3$ (300 mEq $NaHCO_3$ was administrated during entire hospital course).

oped hypotension shortly after ED presentation (blood pressure: 94/52 mm Hg) and remained hypotensive during her hospital stay. Hyperkalemia developed three hours after presentation (potassium: 6.5 mmol/L).

In the CCU, the patient was intubated due to decreased level of consciousness. Although metabolic acidosis resolved with the treatment, the patient developed bradycardia and asystole one hour after intubation. A transvenous cardiac pacemaker was placed. Although capture was achieved, pulse was not obtained. All resuscitation attempts failed and she expired five hours after initial presentation.

Discussion

Easy availability of acid-containing household products has led to an increase in frequency and severity of acid intoxications. Acids are generally available as toilet bowl cleaners (sulfuric, hydrochloric), anti-rust compounds (hydrochloric, oxalic, hydrofluoric), battery fluids (sulfuric), and swimming pool cleaners (hydrochloric) (1).

The highly corrosive power of hydrochloric acid produces immediate coagulating necrosis of the upper digestive tract, resulting in extensive damage. The severity of the lesions depends mainly on the quantity and concentration of the ingested acid, and the elapsed time since ingestion (2). Ingestion of a relatively small amount of hydrochloric acid of 24% or 32% concentration produces immediate and massive necrosis of the upper digestive tract and causes esophageal perforation and mediastinitis, which results in high mortality (3). Our patient reported ingesting nearly 250 mL of hydrochloric acid of unknown concentration.

The presence of acidosis can be used as an indicator of the patient's outcome. Su et al. reported a significantly higher mortality rate for patients with a pH below 7.2 and Vereczkei et al. indicated that a pH lower than 7.0 was a poor prognostic factor (3, 4). Cheng and Kao also reported that an arterial pH lower than 7.22 indicates both severe injury and the need for an emergency salvage operation (5).

The actual cause of blood acidosis in caustic ingestion injury is still unknown. Tissue necrosis resulting in lactic acid accumulation is probably the main reason (6). Theoretically, tissue absorption of the ingested acid agent may contribute to the blood acidosis (5). Since the lactate level was high and hyperchloremia developed, both mechanisms might have contributed to the metabolic acidosis in our case.

The exact mechanism of AMI in our patient as a result of acute hydrochloric acid ingestion is not clear. Myocardial ischemia is essentially a metabolic event. Severe metabolic acidosis may contribute to acute coronary ischemia. Cardiac muscle utilizes adenosine triphosphate (ATP) from aerobic metabolism, which is supplied by glucose and fatty acid metabolism. Unlike skeletal muscle, myocardial muscle does not use anaerobic metabolism. Myocardial functions depend on continue energy supplement because of the myocardium's limited energy reserve (7).

Severe acidemia has major adverse metabolic consequences. It causes increased metabolic demands and reduction in ATP synthesis. These effects on the myocardium are particularly pernicious. Increased metabolic demands result in a higher oxygen requirement. Limited ATP synthesis does not compensate for the higher metabolic demands. Therefore, imbalance between metabolic demand and supply occurs, which results in myocardial ischemia. The detrimental effects of severe acidemia on the cardiovascular system include decreased cardiac output and arterial blood pressure. Re-entrant arrhythmias and a reduction in the threshold for ventricular fibrillation can also occur. Acidemia triggers a sympathetic discharge but also progressively attenuates the effects of catecholamines on the heart and vasculature; thus, at pH values below 7.20, the direct effects of acidemia become dominant. Sympathetic discharge also leads to increased myocardial oxygen demand and ischemia. Finally, brain metabolism and the regulation of its volume are impaired by severe acidemia, resulting in progressive obtusion and coma (8).

However, in our case severe acidemia alone cannot explain the ST segment elevation. Extensive ST elevation on the ECG argues for complete occlusion of an epicardial coronary vessel. It cannot be explained simply by myocardial ischemia due to the metabolic derangements of acidosis. Our patient actually had baseline coronary artery disease, and we conjectured that metabolic acidosis and its systemic effects triggered coronary plaque disruption followed by thrombus formation, which resulted in complete occlusion of a coronary artery. At the time of catheterization, this occlusion may have been resolved, and then ST segment elevation declined.

It is difficult to specify the exact cause of death for this patient. Thirty minutes before she collapsed, her blood gas analysis revealed normal pH and potassium level (Table). Additionally, the ST segment had been normalized and life-threatening arrhythmias such as a ventricular tachycardia or fibrillation had not been detected. Therefore, myocardial infarction would not have been our patient's sole cause of death. Her hematocrit level had declined progressively. She also had become hypotensive in the emergency department and coronary care unit. It is well known that severe acidemia has serious effects on the cardiovascular system; it causes decreased cardiac output and arterial blood pressure (8). Gastrointestinal bleeding could also be responsible for the hypotension and shock that may have contributed to the mortality. Numerous fatal consequences of hydrochloric acid ingestion, such as systemic acidosis and gastrointestinal bleeding, overlapped in our case. Nevertheless, we believe that the AMI played the major role in her fatality.

Airway management, correction of volume depletion and acidosis, early recognition and treatment of possible complications (especially hollow viscus perforation) were the mainstay of the initial stabilization. Gastric lavage and induced emesis were contraindicated because re-exposure of the esophagus to corrosive agent tends to produce additional injury. Activated charcoal was also not recommended. However, in acid ingestion cases that present early, gastric lavage and suction are recommended. The suggestion of gastric lavage for acid ingestion cases that present within 30 minutes after ingestion is based on the idea that it prevents acidosis due to absorption of the ingested acid (9).

The issue of acidosis due to acid ingestion and its aggressive management in the emergency room setting has not been extensively discussed in the medical literature. The literature mainly focuses on gastrointestinal tract injuries and surgical management in the acute care setting and on long-term complications. The adverse metabolic consequences of acidosis may be catastrophic a short time after acid ingestion, as with our case. Early surgical interventions for life-threatening emergencies due to acid ingestion may be necessary, but life-threatening metabolic acidosis should be given high priority in the emergency room setting.

Conclusion

Airway management, correction of acidosis, recognition and treatment of early fatal complications, especially massive tissue necrosis, hollow viscus perforation, acute renal failure, and hemolysis, are cornerstones of acute acid ingestion management. Induced emesis is contraindicated and activated charcoal is also not recommended. In cases that present early, gastric lavage and suction may be recommended to prevent acidosis due to absorption of more ingested acid.

We believe this report to be the first one documenting AMI associated with acid ingestion. AMI may occur as a consequence of acute acid ingestion, and its occurrence may lead to mortality. Physicians should be alert to acute myocardial infarction during the course of acid ingestion, especially in patients with known coronary artery disease or multiple coronary risk factors.

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Special Article

Art at Mount Sinai

Barbara J. Niss, M.A.

Abstract

The Mount Sinai Medical Center in New York is a private institution with many public spaces. Over the years, Mount Sinai has acquired art to add vitality and interest to these public areas. This article provides brief details about some of the larger artworks and how they found their way to Mount Sinai's campus on Fifth Avenue. There is also a description of one smaller object that is held in the collections of the Mount Sinai Archives. The latter is an original sketch of a Mount Sinai physician, done by the famous medical illustrator, Frank H. Netter, M.D.

Key Words: Art; hospital design and construction; Lilienthal, Howard; Netter, Frank; Chermayeff, Ivan; Kozikowski, Nancy; Poor, Henry Varnum; Noguchi, Isamu; Pomodoro, Arnaldo.

The Mount Sinai Medical Center in New York is a private institution with many public spaces. Over the years, Mount Sinai has acquired art, through donation and purchase, to add vitality and interest to these public areas. The reasons for this are many. For one, a hospital is a place where people come for health care. It has long been thought, with some research behind it, that people who are ill or in distress, do better when exposed to beauty (1). Mount Sinai is also a busy workplace, with thousands of employees, medical staff and visitors spending time at the institution. It is of benefit for them too, to have visually stimulating artwork around the Medical Center. And in a larger sense, Mount Sinai is also a part of the urban landscape that is New York City. These artworks help define Mount Sinai's physical space as a landmark in the city.

This article provides brief details about some of the larger artworks owned by the Medical Center and how they found their way to the Mount Sinai campus on Fifth Avenue. There is also a description of one smaller object that is held in the collections of the Mount Sinai Archives. The latter, an original sketch of a Mount Sinai physician, done by the famous medical illustrator, Frank H. Netter, M.D., was transferred to the Mount Sinai Archives by the Department of Surgery. (In general, the dates listed are when the object was put on display at Mount Sinai, not necessarily when the piece was created.)

"Gene Segment" (Fig. 1)
Artist: Ivan Chermayeff (1932–)
Location: Outside the Carl Icahn Medical Institute Building, Madison Avenue
Date: 1998

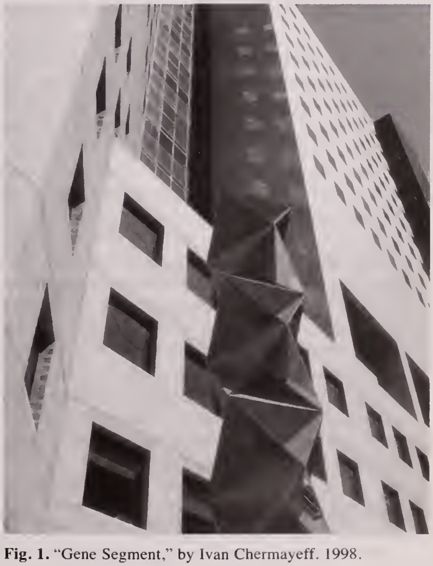

Fig. 1. "Gene Segment," by Ivan Chermayeff. 1998.

Address all correspondence to Barbara J. Niss, Archivist, Levy Library, Box 1102, Mount Sinai Medical Center, 1 East 100th Street, New York, NY 10029-6574.

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As noted in the January 5, 1998 issue of the newsletter, *Inside Mount Sinai:*

> This piece…is an artistic representation and symbol of the cutting-edge research and exploration taking place in the building's laboratories and across our campus. Consisting of orange-colored steel and aluminum forms revolving and rising 28 feet, it is animated by spiraling, mirrored surfaces that reflect the changing seasons, clouds, and people walking by against the background of Mount Sinai's newest building.

The artist, Ivan Chermayeff, is a principal and founder of the New York design firm, Chermayeff and Geismar, Inc. The firm is known for many designs, including the iconic number 9, at 9 West 57 Street in New York and the logo for the Chase Manhattan Bank. Chermayeff studied at Harvard University and the Chicago Institute of Design, and graduated from Yale University School of Art and Architecture. He is an honored member of many professional associations, including the Industrial Designers Society of America and the Alliance Graphique Internationale. Chermayeff has received many honors and awards for his design work.

"Blue Talis" (Fig. 2)
Artist: Nancy Kozikowski (1943–)
Location: Madison Avenue entrance to the Guggenheim Pavilion, over the stairs
Date: 1990

This large piece, 14 feet by 14 feet, was commissioned from the artist while the Guggenheim Pavilion was still under construction. As evident from the title, this work represents a talis, or prayer shawl, invoking Mount Sinai's roots in the Jewish community. Its position on the wall over the stairs makes it a focal point for people leaving the busy Plaza Cafeteria.

Nancy Kozikowski is a well-known textile artist and has been very active in the New Mexico art community. Her main body of work is in weaving, although she has also painted portraits. In her work, Kozikowski explores Native American, Southwestern, and abstract themes, often using geometric shapes. She has been involved in many exhibits and shows, and has pieces in various collections, including the Smithsonian American Art Museum in Washington, DC.

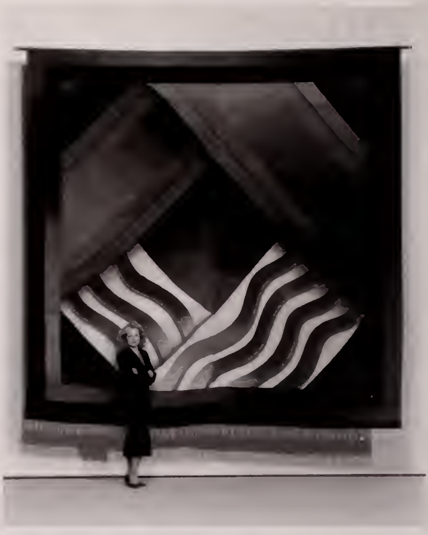


Fig. 2. Artist Nancy Kozikowski standing next to "Blue Talis" in her workshop. 1990.

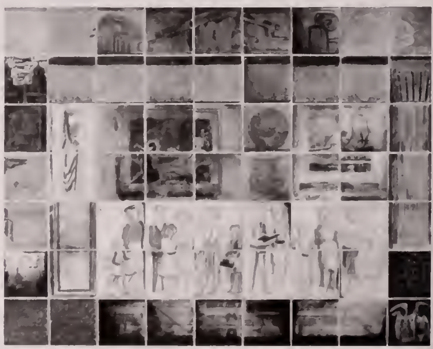


Fig. 3. "Central Park," by Henry Varnum Poor, shortly after its installation in the Klingenstein Pavilion lobby. 1954.

"Central Park" (Fig. 3)
Artist: Henry Varnum Poor (1888–1970)
Location: Lobby of the Klingenstein Pavilion, Fifth Avenue
Date: 1954

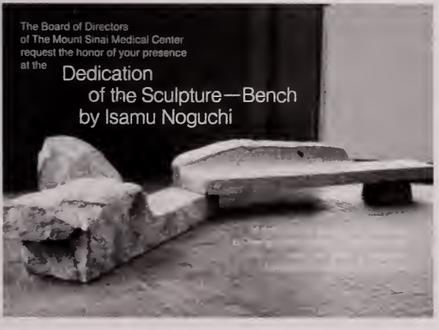
Also known as "Children and Central Park," this large ceramic mural measures almost 8 feet by 19 feet and is composed of almost 250 nine-by-nine inch tiles. It shows scenes of families, the Central Park Zoo, the boathouse and the Metropolitan Museum of Art.

This mural was given to Mount Sinai by the widow of Maurice Wertheim, a Mount Sinai Hospital trustee from 1945 until his death in 1950 at the age of 64. Mr. Wertheim was a founder of Wertheim & Co., an investment banking firm. He was an avid sportsman and chess player, and was committed to environmental causes. In 1947, he donated 1,800 acres of land in Suffolk County on the Great South Bay to serve as a wildlife refuge. As often happens, Mr. Wertheim had many ties to Mount Sinai beyond being a trustee. His daughter, Barbara, was married to long-time Mount Sinai physician, Lester Tuchman. His close friend and one of the executors of his estate was Mount Sinai Chairman of the Board, Mr. Joseph Klingenstein.

The artist, Henry Varnum Poor, was a Phi Beta Kappa graduate of Stanford University, Class of 1906, and received additional art training in Europe. He created art in many mediums. His portraits are in the collections of the National Portrait Gallery in Washington, as well as the Whitney Museum of American Art in New York. Poor worked in ceramics, and authored a book about it. He was also a well-known muralist, creating works for the Department of Justice and Pennsylvania State University. An educator in the field of art, Poor was a founder of the Skowhegan School of Painting and Sculpture in Maine. Henry Poor died in 1970.

Bench (Fig. 4)
Artist: Isamu Noguchi (1904 – 1988)
Location: Southwest corner of Annenberg Building lobby
Date: 1977

This granite sculpture was given to Mount Sinai by Cynthia Hazen Polsky and her sons, just three years after the Annenberg Building opened. It was given in honor of Mrs. Sadie Annenberg, Mrs. Polsky's grandmother, for whom the Annenberg Building is named. The bench is designed to be used as well as admired, and it frequently is.



The Board of Directors
of The Mount Sinai Medical Center
request the honor of your presence
at the
Dedication
of the Sculpture—Bench
by Isamu Noguchi

Fig. 4. The front of the invitation to the dedication of "Bench," by Isamu Noguchi. 1977.

Isamu Noguchi was born in 1904 in Los Angeles, and grew up in Indiana. However, his career was based in New York and he is considered an important sculptor of the New York School. In addition to this stone bench, he is responsible for other recognizable pieces around the city, including *Red Cube*, the painted steel cube on its edge with a hole in the middle outside the Marine Midland Bank at 140 Broadway (1968) and *News*, the stainless steel relief inside the Associated Press Building at Rockefeller Center (1938 – 1940). In 1961, Noguchi moved to Long Island City in Queens, and in 1985 he established the Isamu Noguchi Garden Museum there.

"Sfera Grande" (Fig. 5)
Artist: Arnaldo Pomodoro (1926 –)
Location: Nathan Cummings Plaza, Fifth Avenue side of the Guggenheim Pavilion
Date: 1974

Nathan Cummings, Mount Sinai trustee, 1971 – 1985, commissioned and donated this work to the Medical Center. The founder of the Consolidated Foods Corporation (later the Sara Lee Corporation), Mr. Cummings was an avid art collector and philanthropist. His generosity to Mount Sinai is witnessed today in the Nathan Cummings Basic Sciences Building, the Cummings Atrium and the Cummings Plaza, where the Pomodoro stands. Mr. Cummings died in 1985, but the Nathan Cummings Foundation, established in 1949, continues helping people to this day.

Arnaldo Pomodoro was born in Italy in 1926. A sculptor with an international reputation, Pomodoro did many similar spheres during this period. At the time of the gift, the artist described the work as a "destruction of form," with the breaks in the outer wall an expression of "the potential destructiveness that emerges from our era of disillusionment." The Guggenheim Museum in New York has a smaller sphere by Pomodoro, completed in 1964. The Museum's description of their work also seems to apply to Mount Sinai's *Sfera*:

> Underneath the gleaming skin and solid flesh of the bronze lies a regulating machinery of cogs and gears, which Pomodoro calls "sign systems," akin to the complex interlocking systems of language or of organic bodies. The sphere not only functions as a geometric shape and analogue of a living body or mineral form, but also suggests the globe of the earth. The equatorial rupture produces configurations sug-

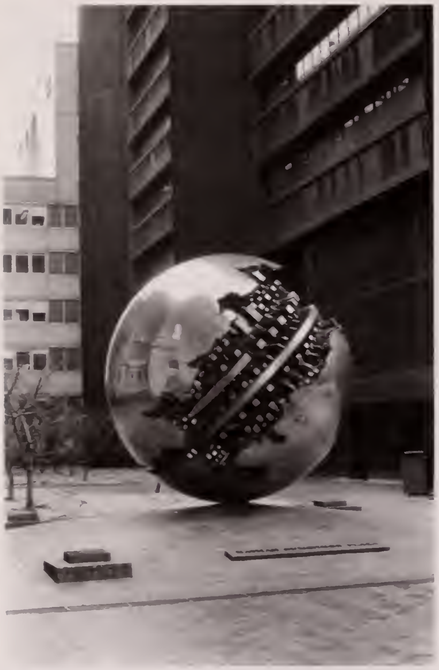


Fig. 5. "La Sfera Grande" in its original home on the Cummings Plaza before the current Guggenheim Pavilion was built. 1974.

> gesting land masses, and evokes the earth's core and desiccated ocean beds. By eliminating frontality, Pomodoro invites the viewer to circle the globe, conveying a sense of uninterrupted rotational movement imitating the orbit of planets (2).

This artwork, perhaps more than any other, has become an important symbol at Mount Sinai. In photographs of the campus, the sphere is often contrasted with the triangular form of the Guggenheim Pavilion. It has also been incorporated as a component of the logo of the Mount Sinai Alumni Association.

"Howard Lilienthal, M.D." (Fig. 6)
Artist: Frank H. Netter, M.D. (1906 – 1991)
Location: In the collection of the Mount Sinai Archives
Date, unknown

Howard Lilienthal was a noted surgeon, inventor, artist and sportsman. He served as chief of Mount Sinai's thoracic surgery service from 1900 – 1922, although he published many papers on general surgical topics as well. He was the medical director of Mount Sinai Hospital's unit, Base Hospital #3, in France in World War I and was cited for the Distinguished Service Medal.

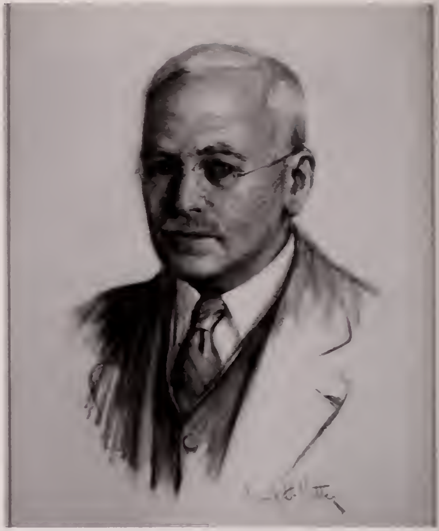


Fig. 6. "Howard Lilienthal, M.D.," by Frank Netter.

Born in 1861 in upstate New York, Lilienthal attended Harvard College and then Harvard Medical School. In 1887, he achieved the top score on the exams for a position on the Mount Sinai house staff, and was the first young doctor in the fifteen-year history of the house staff to choose advanced training in surgery over medicine. In 1925, Lilienthal published an early textbook in English on thoracic surgery, a title that was frequently reprinted. Lilienthal died in 1946 at the age of 85.

The artist, Frank H. Netter, M.D., was born in Brooklyn in 1906 and became a successful commercial artist in the 1920s. Then, at his mother's request, he enrolled in the New York University School of Medicine, graduating in the class of 1931, and served a two-year surgical internship at Bellevue Hospital. In 1933, he joined the staff of the Mount Sinai Hospital Out Patient Department, working in the general surgery clinic. He continued working as an artist to support himself as he tried to start a practice. By the end of the 1930s, Netter had combined his two careers into the field of medical illustration, and over his lifetime achieved considerable recognition for his work. It would be hard to find a doctor who trained in the second half of the 20th century who had not studied a medical illustration by Netter.

Netter is best known for a series of projects begun after World War II with the CIBA Pharmaceutical Company, which culminated in the multivolume set of *The CIBA Collection of Medical Illustrations*. This work, arranged by organ system, required months of studying before the drawings for each volume were begun. Although Dr. Netter died in 1991, his work continues to be used and is currently available in digital format.

For additional information about the artwork described here or about Mount Sinai's history in general, please contact the author at the Mount Sinai Archives.

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Neurological Notes

The Neurological Implications of Fibromuscular Dysplasia

Lloyd A. Dayes, M.D., and Nalini Gardiner, M.A., Ph.D.

Abstract

Fibromuscular dysplasia is a noninflammatory segmental disease of the arteries, of unknown origin. While the renal arteries are most commonly affected, other larger vessels, including the carotid and vertebrals, may be involved. Fibromuscular dysplasia has been implicated as a cause of stroke in adults and (on rare occasions) in children. The classic angiographic presentation is that of a string of beads. The condition frequently requires surgical or interventional radiological treatment. These approaches most commonly lead to long-term neurological improvement. Five cases with typical angiographic appearance are presented.

Key Words: Cerebrovascular accident, hypertension, fibromuscular dysplasia.

In 1938, Leadbetter and Burkland (1) published the first report of fibromuscular dysplasia (FMD) of the human vascular system. They described it as a nonatheromatous segmental disease of the renal arteries. About a quarter century later, Palubinskas and Ripley (2) reported angiographic evidence of this disease entity in the literature, citing autopsy and surgical histologic findings. FMD is a nonatherosclerotic, noninflammatory condition involving elastic, muscular and fibrous elements mainly of the extracranial vessels. Involvement of both cervicocranial and renal vessels with FMD carries neurological implications. Such involvement may also cause: (a) secondary hypertension when the renal arteries are involved; (b) the stuttering, stroke-like syndromes, i.e., transient ischemic attacks (TIAs) and, at times, progressive stroke resulting from occlusive FMD of the cervicocranial vessels; or (c) associated aneurysm which may rupture and produce the devastating effects of subarachnoid hemorrhage. The constellation of signs and symptoms runs the gamut from the common complaint of dizziness to TIAs, intracerebral hemorrhage, rupture of an intracranial aneurysm, or occlusion of a major cerebral vessel.

FMD is an uncommon vascular disorder that occurs in young to middle-aged individuals, especially women. The disease consists of a heterogeneous group of histologic changes, which ultimately lead to arterial narrowing. Clinical manifestation reflects the arterial bed involved, most commonly hypertension (renal) and strokes (carotid). Fibromuscular dysplasia is a pathological diagnosis in the appropriate clinical setting. This noninflammatory disease is a common mimic of vasculitis.

While this disease is principally found in the extracranial vessels of the cervical region, it may affect other arteries of the body, including the renal and coronary arteries. Sudden death in a previously healthy individual may, at necropsy, show myocardial infarction caused by occlusion of a vital coronary artery by FMD, again emphasizing the lethal nature of this disease. Sudden, unexpected death may occur during exercise, and the patient may have had no previous cardiac history. At autopsy, there may be marked intramural coronary artery dysplasia of the ventricular septum, which may be accompanied by myocardial fibro-

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From the Department of Neurosurgery, Loma Linda University Medical Center, Loma Linda, CA.

Address all correspondence to Lloyd A. Dayes, M.D., Division of Neurosurgery, University Medical Center, 11234 Anderson Street, Loma Linda, CA 92354.

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sis. The arterial dysplasia can be characterized by severe medial thickening, with smooth muscle cell disorganization and marked luminal narrowing. There may be no evidence of myofiber disarray or asymmetric septal hypertrophy to suggest hypertrophic cardiomyopathy. There may also be no associated cardiac or extracardiac lesions found at complete autopsy of these individuals. It can be concluded that small vessel disease of the intramural coronary arteries of the ventricular septum may be an isolated finding leading to sudden cardiac death in young adults.

In reported cases of fibromuscular dysplasia, the preponderance is women:men in the ratio of 6:1. Surgical intervention is frequently necessary, but antithrombotic agents may be an alternative when patients prefer to avoid surgical or interventional radiological treatment.

Case Reports

Case 1

A 58-year-old Caucasian female presented with a sudden onset of aphasia and an associated left-sided paresis and hypesthesia to pinprick, maximal in the upper extremity. Historically, she had several prior episodes of left hemiparesis but no prior aphasic episodes. All neurological symptoms regressed within 24 hours. Subsequent angiography revealed fibromuscular dysplasia of the right internal carotid artery over a 4 cm segment. She was treated with aspirin and dipyridamole, and has been asymptomatic since investigation.

Case 2

A 65-year-old female presented with transient visual disturbances consisting of central scotomata. Each episode lasted approximately ten minutes and was associated with a fuzzy feeling in her head or slight dizziness. The first episode was three months prior to investigation. Angiography demonstrated bilateral distal internal carotid artery FMD. Conservative medical care was given.

Case 3

A 74-year-old female presented with complaints of transient episodes of right-sided numbness, right arm transient paresis, lightheadedness, headaches, nausea, and occasional vomiting. Dysplasia of the left internal carotid artery was found at angiography.

Case 4

A 76-year-old female complained of transient episodes of feeling faint—as if she would "black out"—although she never lost consciousness. She also complained of numbness and tingling in her upper extremities for 1 – 5 minute periods. Angiography showed bilateral carotid FMD. She was placed on a regimen of aspirin and dipyridamole and has done well since initial evaluation.

Case 5

A 66-year-old, right-handed Caucasian male presented with a history of progressive mental deterioration characterized by confusion and poor memory retention. In addition, he reported a long history of right facial pain and right occipital neuralgia. Previously, he had undergone a right subtemporal craniotomy for partial obliteration of the right Gasserian ganglion, with a subsequent right facial hypesthesia. Computerized tomography of the brain showed a multiple infarct pattern of low densities, more prominent in the right hemisphere than the left. Cerebral angiography revealed bilateral internal carotid and left vertebral FMD (Figure). The right vertebral artery was not visualized.

Discussion

The clinician depends primarily on angiography for the diagnosis of fibromuscular hyperplasia, either renal or cervicocranial. The medical or surgical neurologist who evaluates patients with TIAs will occasionally encounter a patient who has no evidence of occlusive disease but has the stigmata of FMD. There may be stenosis or turbulent blood flow and consequent platelet aggregation resulting in platelet embolization to the intracranial vessels.

FMD may be associated with intracranial aneurysms. There may be a systemic dysplasia of vessels including the renovascular system. When the latter is affected, hypertension ensues, making the likelihood of subarachnoid hemorrhage from ruptured aneurysm a greater possibility. The disease may affect splenic, celiac, mesenteric, axillary, and other extracranial arteries, including the superficial temporal, as noted by Patchefsky and Paplanus (3). Hartman et al. (4), in 1971, reported the case of a 29-year-old female with generalized FMD and bilateral internal carotid artery occlusion. She had been taking oral contraceptives and was also on anticonvulsants. Whether or not the medications and the progression of her disease were related is unclear. Her regimen becomes significant, however, in an age when oral contracep-

Figure. Note "string of beads" appearance of distal vertebral artery.

tives have been implicated in the genesis of strokes.

Visually, FMD has been described as a "string of beads," the most common location being the distant two thirds of the internal carotid and the renal arteries. Pollack and Johnson (5) emphasized that the tubular form of FMD may be mimicked by diffuse carotid artery spasm following arteriographic manipulation. The latter, however, will disappear with time, contrasting with the permanence of the dysplastic changes.

From the reports of Kincaid et al. (6), there is evidence that internal radiographic examination shows progression of the disorder in at least one third of their cases. The accepted classification of FMD follows four subdivisions, based on the pathologic findings:

1. Arteries with only fibroplasias of the intima,
2. Maldevelopment or malformation of the media, with fibrosis and thinning of the arterial wall and resultant aneurysm formation,
3. Fibromuscular changes associated with disorganized muscle fibers and fibrosis, and
4. Collagenous changes with ring-like constriction around the media. These changes are segmental, affecting small and medium-sized vessels, especially those that are paired.

The affected arteries frequently show cushion-like outpouchings of the intima. Occasionally, arterial dissections have been seen. At the present time, there appears to be no plausible explanation for FMD, and speculation has included a congenital etiology, inflammatory origin, or even classification with the collagen diseases. Hormonal factors have also been suggested, particularly since there is a definite female preponderance.

The surgical correction of FMD (7) may be accomplished by end-to-end anastomosis after resecting the diseased portion of vessel, vein graft anastomosis using autogenous saphenous vein, arteriotomy, artificial graft anastomosis, and resection of fibrotic tissue from the affected section of artery. The use of stents by the vascular radiologist is a popular new method for treating FMD of the carotid arteries. It has been very effective in treating the major vessels of the trunk and periphery, but especially the carotid arteries. In general, early detection of this vascular disorder followed by appropriate treatment increases the likelihood of a satisfactory outcome.

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Letter to the Editor

To the Editor: In your May issue, Khan et al. (1) reported a case of internal carotid artery dissection (ICAD) with associated oculosympathetic palsy, which followed chiropractic manipulation (CM) that had been performed one day earlier. However, it had previously been reported that the medical literature does not support a clear causal relationship between CM and ICAD (2). There are often confounding factors, such as connective tissue abnormalities (3), underlying arteriopathies (4), hyperhomocysteinemia (5), or coexistent infections (6), any of which may obscure a cause-and-effect relationship.

Based on two epidemiological studies that reported the incidence of ICAD at 2.6 and 2.9 cases per 100,000 population yearly (7, 8), nearly 8,000 ICADs are estimated to occur in the United States each year. Since the typical ICAD patient experiences prodromal symptoms that include headache and neck pain, it is likely that a proportion of these 8,000 patients will consult chiropractic physicians in the days, weeks, or months before the ultimate ICAD diagnosis. The mere fact that an ICAD develops at some point in time following CM does not establish a causal relationship. A causal relationship may exist in cases where head or neck pain with ensuing ischemic signs develops immediately following or within hours after CM, but because of the widespread uncertainty concerning the etiology of ICAD (9, 10), there will always be a measure of doubt about the true cause.

Stringer and Kelly (11) propose a mechanism for traumatically induced ICAD that involves a sudden, severe stretch of the internal carotid artery over the upper cervical spine when the neck is hyperextended and laterally flexed to the opposite side. However, CM is a highly specialized procedure which is the focal point of a chiropractic physician's education and no CM maneuvers that resemble this description are taught in any of the chiropractic institutions in the U.S., to our knowledge. Violent long-lever manipulations may sometimes be used by untrained manipulators, which may be the reason that non-chiropractic providers have been responsible for a disproportionate share of reported cases of ICAD following manipulation (2, 12).

Khan et al. suggest in their conclusion "...that patients with neck pain be examined and neuroimaged in order to exclude possible underlying pathologies before receiving any manipulation of the neck." This suggestion is unreasonable, given that the odds of developing ICAD that is temporally related to CM has been estimated at approximately 1:601,145,000 (2). Moreover, ionizing radiation itself may pose a health hazard, creating an unfavorable risk-benefit scenario for obtaining the image.

Michael T. Haneline, D.C., M.P.H.,
Associate Professor
Robert Cooperstein, M.A., D.C. Professor
Palmer College of Chiropractic West
90 East Tasman Drive
San Jose, CA 95134

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Authors' Response: Haneline and Cooperstein point out in their letter that a causal relation between chiropractic manipulation (CM) and internal carotid artery dissection (ICAD) is only likely if symptoms of oculosympathetic palsy occur immediately or within "hours."

In the present case, it is impossible to quantitate the exact time interval between CM and ICAD, since the patient awoke with symptoms the morning following the manipulation. Therefore, we suspect that the symptoms of ICAD may well have begun in closer temporal proximity to the CM than can be quantitated. In other words, though the left eyelid droop was first noted the "following morning," the onset of the ICAD undoubtedly occurred at some earlier time, most likely while the patient was sleeping.

ICAD is clearly a rare complication of CM. Our case report implies that there may well be a causal link in some patients and that physicians should be aware of this possibility. We also continue to believe that it would be prudent to perform neuro-imaging when CM is required repeatedly or when there are other possible risk factors for dissection, including poorly controlled hypertension or known cerebrovascular disease.

To conclude, we agree that it is difficult to prove a causal association from only a case report, as proving causation generally requires well-controlled studies. Nevertheless, given the strong temporal relationship between the cervical chiropractic manipulation and carotid artery dissection in this patient, a coincidental association appears less likely. Furthermore, other studies have also reported a similar temporal association between cervical manipulation and carotid artery dissection (1–5).

Amir M. Khan, M.D., Mark A. Korsten, M.D.,
Alan Rosman, M.D.
Mount Sinai School of Medicine
VA Medical Center
Bronx, NY

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Melvin D. Yahr (1917–2004):

A Life Dedicated to Parkinson's Disease and Neurology

This tribute to Dr. Yahr was the subject of a Grand Rounds Lecture on December 14, 2004.

It was only a year ago that Dr. Melvin Yahr introduced as a speaker, in a special lecture and grand rounds, a long-time friend of his and one of his great intellectual partners, Dr. Arvid Carlsson, the 2000 Nobel laureate who first demonstrated that Parkinson's disease is characterized by a loss of dopaminergic innervation.

This discovery, made in the 1960s, led to what is still the most effective treatment of the disease, using the dopamine precursor L-dopa. The steps from identifying the biochemical defect to translating the discovery into an effective treatment were arduous, and Melvin Yahr was among the very first not only to conduct laboratory and clinical experiments with dopa, but to apply his clinical scientific knowledge to refine the form of dopa that could be tolerated (L-dopa), and to conduct the first controlled trials of the drug. He was also one of the first to recognize that this miraculous treatment for Parkinson's had long-term complications, e.g., the motor response fluctuations and dyskinesias, phenomena that remain puzzling and unexplained.

I had the good fortune of working with Dr. Yahr, first during my residency at Mount Sinai, when he was chairman of the department, and then as his fellow in Movement Disorders in 1991–1993. Like many other neurologists that he trained in his long career, I quickly learned that behind his serious and challenging personality there was a man of encyclopedic knowledge and passion for his work, with an ardent scientific curiosity that he would apply to clinical cases presented to him on rounds or to scientific or theoretical questions on the brain.

Generation after generation of his students retain the fondest memories of Dr. Yahr, not only for his clinical and scientific acumen and achievements, but also for his exemplary and uncompromising ethics, loyalty, empathy, and great love of humanity.

At times, after rounds or after seeing patients, he would share stories of his earlier years, including childhood memories of anti-Semitism, memories that instilled in him his sense of social justice and the need for physicians to be engaged in the fight for civil rights and health care rights. Among his little-known achievements was his early support for women and minorities in academic medicine, and his lifelong fight for the rights of patients to receive the best medical care regardless of their social and economic status.

A native New Yorker, Dr. Yahr graduated from New York University Medical School in 1943 and completed his residency at Montefiore Hospital. After serving in the armed forces he joined the Department of Neurology at Columbia University, where he built the first Parkinson's disease center, a legacy that continues to this day. In 1973 he stepped down from the positions of associate dean and Houston Merritt Professor of Neurology at Columbia to become chairman of Neurology at Mount Sinai, a position that he held until he retired in 1992. He remained active as chairman emeritus and professor of neurology until his death.

In addition to his fundamental role in the creation of the field of Parkinson's disease, Dr. Yahr established the first NIH-funded Clinical Research and Education Center in the US, which he led for more than 20 years. He also served as president of the American Neurological Association and the American Board of Psychiatry and Neurology, was on the editorial board of many scientific journals, and was chairman of the board of trustees of the Association for Research in Nervous and Mental Disorders. He played an essential role in the creation of the Parkinson's Disease Foundation, and subsequently founded the World Federation of Neurology Committee on Parkinsonism and Related Disorders, which he led until 2001. The many awards and honors that he received from universities around the world offer further testimony to his role in creating and defining the field of Parkinson's disease.

He will be missed at Mount Sinai, in the Parkinson's disease community, and in the neurological and scientific world at large. It will be the duty of us, his students, to carry into the future his passion, humanity, and visionary sense of care and intellectual pursuit.

Alessandro Di Rocco, M.D.
Albert Einstein College of Medicine
650 First Avenue
New York, NY 10016
adirocco@aecom.yu.edu

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